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APRIL, 1925

ORIGINAL ARTICLES.

PAIN PHENOMENA OF THE FACE, THEIR ORIGIN AND TREATMENT WITH SPECIAL REFERENCE TO TRIGEMINAL NEURALGIA.

By Charles H. Frazier, M.D.,

PHILADELPHIA.

(Read before the Section on Oral Surgery of the First District Dental Society of New York, October 22, 1924.)

The consideration of sensory disturbances in the region of the face, more particularly pain phenomena, at once opens a field in which there is abundant opportunity for discussion—a discussion which if followed beyond a very superficial study, takes us into the realm of comparative as well as human anatomy and physiology. While attention will be focused chiefly on *major* trigeminal neuralgia we cannot disregard other forms of painful affections, which in their persistence and in their severity as measured by the patient, are equally distressing and command our attention.

In the region of the face the predominant nerve of sensation is the trigeminal, but it must not be forgotten that in the facial nerve also there are sensory fibers and that at least some parts of the sympathetic system, as in the visceral distribution, perform a sensory function.

Primarily the entire function of the nervous system was represented by sensory and motor structures whose nuclei were distributed throughout the spinal axis, but as the brain became differentiated certain groups of spinal cells, both motor and sensory, became the nuclei of the cranial nerves.

The trigeminal and facial nerves operate physiologically in the same territory, and if studied phylogenetically, we find in the lower

forms of animal life a close alliance between them. Thus in the aquatic lower vertebrates the facial receives a large reinforcement of sensory fibers, part of a septum of cutaneous end-organs. Some of these, as in fishes, serve for the perception of pressure sense. Furthermore in the primitive forms (amphibian group) the root fibers of the facial nerve are often so intermingled with those of the trigeminus that it is difficult or impossible to differentiate, in their course from their nuclei to the points of emergence from the pons, the fibers of these two nerves one from the other. Not only therefore are their nuclei in close proximity, but their fibers intermingle.

In the consideration of pain phenomena of the face, should one overlook the sympathetic system? For some reason or other, throughout the trigeminal tract nature made abundant provision for sympathetic control or association; for example there are the sympathetic fibers from the internal carotid plexus to the Gasserian ganglion, there is the ciliary ganglion of the ophthalmic division, the sphenopalatine of the maxillary division and the otitic and submaxillary ganglia. These rich sympathetic connections may not be without their significance. Operations upon the cervical sympathetic ganglia have been practised many years for the purpose of relieving pain as in trigeminal neuralgia and migraine. I will not discuss these now, but would like to call your attention to the fact that when one stimulates electrically the cervical sympathetic ganglion or the periarterial sympathetic plexus of the common carotid artery, as I have a number of times in operations on the neck under local anesthesia, the patient frequently complains of pain within the zone of the trigeminal distribution.

The major theme of our discussion has to do specificially with major trigeminal neuralgia, and while in most instances this disease is readily recognized by the mere recital of the patient's history, there are other forms of neuralgia with which it may sometimes be confused. The term neuralgia obviously implies pain and yet there are of course many degrees of pain. A moderate degree of surface pressure might lead to discomfort but if continued with increasing force it may readily elicit pain, but the precise point at which this transition between discomfort and pain takes place would be difficult to determine, and can be interpreted only by the patient. And so with all neuralgias we are dependent entirely upon the patient's description and upon his estimation in his own terms, of the degree of pain. As pain is a subjective phenomenon we have no means other than the patient's statement as to the intensity of his suffering. The possibility therefore, of being misled by exaggeration either intentionally or unintentionally on the part of the patient, must not be forgotten, and we must be on our guard especially in neurotic subjects and drug addicts lest we be persuaded to resort to such radical procedures as the circumstances may not justify.

The significant features of these neuralgias obviously is the almost purely subjective character of the symptoms. There are, with some exceptions, no objective signs upon which a differential diagnosis may be established. One must listen patiently to the story and the description as told by the one afflicted and have the account repeated often in order that the clinical picture may be clear and not confused. Sometimes it is difficult, if not impossible, from the patient's own words to secure a picture clear enough to satisfy the examiners. The more confused and indefinite the picture, the more the pain expression varies in character and location in the individual case the surer one can be that the neuralgia belongs not to any one of the more definite types, such as tic douloureux or herpetic neuralgia, but to that miscellaneous medley of pains and discomforts which baffle us ofttimes both as to diagnosis and treatment.

Just as there are many degrees, so there are many kinds of pain. In our analysis of 1025 cases of neuralgia that have been observed in the Neurosurgical Clinic of the University of Pennsylvania Hospital, without any preconceived notion as to classification, we found at least three different types of sensory disturbance: (1) Pain sensation, using the term in its descriptive sense as opposed to other forms of sensation such as tactile, thermal or pressure; (2) pressure sensation, and (3) thermal sensation. Presumably it is reasonable to postulate that in a lesion of any sensory nerve there may be disassociation of sensation, so that it is not surprising to find in a lesion of the trigeminus these varying expressions of disturbed sensation, classified as they are under pressure, thermal and pain. For example, under disturbance of thermal sensation we might include, "burning," "smarting," stinging" pains, or, to use a not infrequent descriptive phrase, "the feeling of a hot iron." Under disturbance of pressure sensation could be included "boring" "grinding" "squeezing" or "drawing" pain; and under disturbance of pain sensation, using the word in the technical sense again as of that of a cutting instrument, "stabbing," "cutting," "sharp," "pricking," and "piercing."

But to what end is this sketchy review of the problems relating to the source and to the character of painful phenomena in the face? It may serve a useful purpose if only by bringing into relief the variability of these phenomena, the obscurity of their origin and the need for continued and painstaking observation in the hope that they will bring to light certain aspects of these painful nerve lesions that are now obscure.

From this more or less theoretical discussion, we turn now to a systematic review of the various forms of neuralgia to be considered in a differential diagnosis.

1. There is in the first place the neuralgia that is a sequel to infection as of the teeth or sinuses, a neuralgia due in all probability to a peripheral neuritis, to an inclusion of the peripheral or terminal

filaments of the trigeminal nerve in the inflammatory process. I need scarcely more than refer to it, as you are familiar with this commonplace ailment. The pain, originating with infection, is more or less constant, often throbbing in character and subsides with the subsidence of the inflammatory process. Above all, be it said that the pain is not paroxysmal, coming and going with intervals of complete freedom. At no time should there be any reason for confusing this form of neuralgia with the so-called tic douloureux.

2. Then we have the postherpetic neuralgias. There has been an attack of herpes zoster or "shingles" in one or the other branch of the trigeminus, more frequently the supraorbital, and the pain is of greatest intensity during the "zoster" attack. Again the pain is not paroxysmal but more or less constant with perhaps exacerbations. One of the conspicuous and distinguishing features of postherpetic neuralgias is hyperesthesia of the skin.

3. There are the neuralgias, relatively infrequent to be sure, that accompany tumors of the Gasserian ganglion and of all the facial neuralgias, these are most likely to be confused with the major trigeminal form. But there are certain distinctive features which, if recognized at once, serve as signs of differentiation. I refer particularly to certain *objective* disturbances of the skin and especially to hypesthesia, observed first in the cornea.

4. There are certain painful phenomena of the face (neuralgia is not an appropriate or descriptive term, although usually used in this connection), which are associated with the hemicranias or migraine. The vasomotor disturbances, one sees in the truly migrainous subject, as expressed by the sudden pallor or sudden flushing of the face, by the pupillary dilatation, by the salivation, are distinguishing features.

5. Second in frequency is that group of miscellaneous neuralgias which, for a better understanding either as regards to origin or treatment, we call "atypical," very much as we applied at one time the term "idiopathic" to certain forms of epilepsy, the origin of which was obscure. These "atypical" neuralgias are not due to infection, as of the sinuses though many a sinus has been drained in the vain hope of relief. As compared with other forms of neuralgia and particularly with tic douloureux, there are many distinguishing features. The pain is not referred to the periphery, as to the lips, chin, alae of the nose, is not related to anatomic zones, as to one or the other supplied by branches of the trigeminal nerve, it may and often does extend beyond the trigeminal territory, as to the neck, submaxillary or retromastoid region. Pain, referred chiefly to the malar region, the orbit and temple, usually is described as pulling or drawing, as boring or as an ache. The sense of pressure or tension often seems predominant. It is constant, not paroxysmal, worse by night rather than by day and may be relieved by opiates.

Carry this picture in your mind and at once you will differentiate it from the next and last group.

6. Major trigeminal neuralgia, tic douloureux, epileptiform neuralgia, la grande neuralgie, surgical neuralgia, trismus dolorificus, an array of descriptive terms giving in themselves a composite picture of the kind of neuralgia they designate. I need not enlarge upon the clinical characteristics of a disease, described as long ago as 1776 quite as accurately as though the description were written today. Suffice it to say that a diagnosis of major trigeminal neuralgia should not be considered justifiable first, when there is an associated area of hypesthesia or anesthesia in the trigeminal zone; second, when the pain is continuous and not paroxysmal; third, when in the early stages there are not intervals of complete freedom; fourth, when the pain does not correspond to the anatomic zones, and last when the pain is not referred primarily to the terminal areas of nerve distribution.

Did time allow I should like to discuss the etiology of these several forms of neuralgia. In some forms the cause is quite obvious and in some the discussion would take us far afield in the realm of speculation. As major trigeminal neuralgia is of particular interest to the oral surgeon, I will say a word as to its etiology with reference to infection. It has been said frequently that inasmuch as peripheral injections will temporarily relieve pain and ergo, the lesion in major trigeminal neuralgia must be peripheral and if peripheral what more likely cause than an infection of the terminal filaments of the trigeminal nerve with an ascending neuritis. Hence oral sepsis and sinusitis, as the most common manifestations of infection in these zones, have been held by many as the responsible causative agents.

Realizing full well that the burden of proof rests on the shoulders of one who entertains the central theory as to the origin of the disease, I have never been weaned away from this hypothesis. Whether there is any justification for the central theory at least this may be said to refute the peripheral theory. First, as to oral sepsis, let me say that the elimination of this by the extraction of carious teeth or the removal of apical abscesses, *never cured* a single case of major trigeminal neuralgia. If there are any exceptions to this sweeping statement, they have never been brought to my attention in the hundreds of cases that have passed through our clinic. And if there be any force in argument by numbers, in not a single instance have I been convinced that a sinus infection was the underlying cause. And here, as with oral sepsis, when a sinus was suspected of infection the drainage of that sinus or the extraction of teeth never cured the disease.

I admit, that in a number of cases, sinuses have been drained on very flimsy evidence of infection, just as thousands of teeth have been extracted without any evidence of oral sepsis. Whenever you

hear or read of a case in which the patient is alleged to have been cured of major trigeminal neuralgia by sinus drainage you may be quite sure that the neuralgia, from which the patient suffered, is not the major trigeminal neuralgia as you and I understand the term.

I decry, as others do, the practice of extracting sound teeth *ad libitum*. Almost every day one sees a patient who has had more than one sound tooth extracted, many patients who have had all the teeth on the affected side, in upper or lower jaw, and not a few with all the teeth extracted in both upper and lower jaw on the affected side, or on both sides.

From the standpoint of etiology the "atypical" neuralgias offer an interesting field of study. As a group the clinical earmarks are very much more varied than those of the major type or tic douloureux. In the latter the differential diagnosis is only exceptionally attended with doubt. Usually the diagnosis is established as the patient relates the story of his illness in the course of which, incited by talking, one of the characteristic paroxysms is easily recognized by the fixed expression of the face, the champing movements of the jaw, the vasomotor flush, lacrymation, the appearance of great suffering. At the onset of a paroxysm the patient suddenly stops talking in the middle of a sentence, in less than a minute the paroxysm is over and he resumes his story.

In the "atypical" neuralgias the pain is continuous and frequently described as a burning or as a sense of pressure; it is deep seated, not superficial; the tissues are described as under great tension as though they would burst. The picture is quite constant; years may have elapsed since the onset but the picture is always the same; it is always a unilateral affection and the pain or discomfort is referred to very definite and unchanging zones. For the past two years, we have made a more or less intensive study of the disturbances of sensation in the trigeminal and facial nerves and cervical sympathetics, in the hope that having defined the function peculiar to each of these nerves we may find a reasonable explanation for these atypical cases. We have examined many cases after the trigeminal nerve has been paralyzed by section of the sensory root, cases of paralysis of the facial nerve alone and in combination with trigeminal anesthesia; cases after section of the cervical sympathectomy alone and combined with section of the sensory root, and a few in which all three nerves have been paralyzed. With these various combinations an unusual opportunity has been offered to study the various forms of sensation which might be attributed to these several nerve distributions.

We admit, at once without any qualification, that insofar as relates to sensation of the cutaneous or mucous surfaces pain sense, thermal and tactile sense preside in the fifth or trigeminal nerve. And without qualification we may add that we have not discovered

any objective disturbance of sensation that might in any way be related to the cervical sympathetics. We find ourselves unable to speak so definitely when we come to consider pressure sense. In the first place pressure sense must be distinguished from the sense of pain on pressure. After section of the sensory root the sense of pressure is preserved but pressure pain is lost. The patient may feel the pressure of the instrument at 4 kg. but no amount of pressure after section of the sensory root will elicit pain. Curiously enough, we have found pressure sense disturbed only when both the trigeminal and facial nerves are completely paralyzed.

Thus our observations on the sensory function of these three nerve tracts, singly and in combination, failed to give us a clue as to the explanation of these atypical neuralgias. They have, as we have noted repeatedly, one outstanding characteristic—the pain or discomfort is usually deepseated and confined to a territory that does not correspond to any particular nerve distribution. In groping about for a clue the suggestion was made that the pain distribution might correspond to some vascular zone and with this in mind one of my staff (Fay) has been studying the problem with mercurial injections of the internal maxillary and facial arteries.

Leaving these speculative considerations, we will conclude our presentation with a brief *résumé* of our experience in the treatment of the major form of trigeminal neuralgia. For many years we have relied solely: (1) Upon alcoholic injections of the second and third divisions with an occasional injection of the ganglion, and supra-orbital nerve; (2) upon the radical operation, section of the sensory root and of the two the injection method, to be successful, requires more experience than the operation. An alcohol injection to be effectual implies the injection within the nerve substance of $\frac{1}{2}$ to $\frac{3}{4}$ cc of alcohol. In inexperienced hands, many bizarre attempts have been made to inject these nerves with anything but satisfactory results and at times with harmful results. When patients have had alcoholic injections before they have come under our care, we find upon questioning that following the injection there has been no zone of anesthesia. This at once stamps the injection as "ineffectual." A successful injection implies not only the immediate relief of pain but also a zone of anesthesia in the distribution of that particular division. With these qualifications, we may assure the patient relief from six months to two years, sometimes longer.

With the understanding that there are but two and only two methods of relief, the alcoholic injection, with its transitory relief, and the radical operation, the patient is allowed to elect which of the two therapeutic procedures he will take. The patient when first seen, having had no experience with alcoholic injections, invariably choses the injection treatment and, *vice versa*, having had 3 or possibly 4 injections, he invariably elects the operation. There is abroad still a misunderstanding of the immediate and ulti-

mate effects of the radical operation. There are many in the profession today who labor under the impression that it is disfiguring, dangerous and a more or less desperate undertaking, to be reserved as the last resort. As many of these cases of trigeminal neuralgia originate in your practice, it is only proper that you should know the truth. In the first place, as the scar is entirely concealed within the hair line, the cosmetic results are perfect. The risk of operation has been so minimized that the mortality is less than half of one per cent. We have performed over 300 major operations in the clinic; in one series of 153 cases there were no deaths and in another of 205 consecutive cases only 1 death. The operation, therefore, is neither disfiguring nor dangerous. We have modified the technic in such a way as practically to eliminate corneal keratitis as a complication. The patient must be advised that a considerable area, contracting somewhat with time, of numbness or anesthesia will follow the operation. This is unavoidable but you will never see a patient with this agonizing pain who is not willing to exchange the pain for numbness. So you should be prepared to allay in your patient the fears and apprehensions bred of misunderstandings and ignorance. Of all the forms of neuralgia, the major trigeminal form is the only one for the relief of which we have an accepted and effective remedy.

Summary. To view comprehensively the disturbances of sensation, as expressed in the neuralgias of the face, one must bear in mind three possible sources of sensory supply, the trigeminal nerve, the facial nerve, and possibly the sympathetic. Studied phylogenetically, we find in the lower forms of animal life a close alliance between the facial and trigeminal nerves, both as to their nuclear origin and peripheral course and distribution. Throughout the trigeminal tract there is an abundant provision for sympathetic control or association. These sympathetic connections may not be without their significance.

The varieties of sensory disturbance, as seen in the neuralgias, typify different forms of sensations, including pain, pressure, and heat. In the trigeminal nerve, as in other nerves with sensory fibers there should be, as there appears to be, disassociation of sensation. A study of patients with paralysis of the trigeminal, facial and sympathetic singly and in combination has been made to allocate their different forms of sensation. The differential diagnosis between the atypical and typical neuralgias and especially major trigeminal neuralgia is essential in the decision for or against the major operation.

Whatever may be the cause of major trigeminal neuralgia, infection plays no part. The pain is relieved only by two measures, alcoholic injection and section of the sensory root. The latter, or major operation is almost devoid of risk. The author has performed over 300 major operations, the last 205 with only 1 death.

THE BLOOD PLATELETS IN THE LEUKEMIAS.*

By George R. Minot, A.B., M.D.,

and

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Boston, Mass.

(From the Medical Service of the Collis P. Huntington Memorial Hospital of Harvard University.)

The blood platelets, formed elements derived from the megacaryocytes of the bone marrow, are known to fluctuate markedly in the leukemias. In lymphatic leukemia it is characteristic to find them decreased, due presumably to a crowding out of their parent cells by lymphoid elements. The megacaryocytes are deeply implicated in the disease of the myeloid tissue known as myelogenous leukemia, so that both increased and decreased numbers of platelets occur in the peripheral blood. So many platelets and even megacaryocytes may appear in the blood stream[1] as to suggest in a rare case that the platelet-forming tissue is affected much more than the leuko- or erythroblastic tissue. In appraising the state of health of a patient with leukemia or apprehending his future, important information may be obtained from the histology of the blood, as well as serviceable knowledge from the history, physical examination and basal metabolism. A comprehensive determination of the character and numbers of white cells is of the greatest value, and a study of the state of the red cells gives useful knowledge. The blood platelets, though of less importance, are not to be neglected in determining prognosis. In the literature, except for an occasional brief note, such as given by Vogel,[2] statements are wanting which emphasize the information to be obtained from observation of the platelets in leukemia.

Material and Technic. During the past ten years an opportunity has been taken to study the blood platelets in some 75 cases of chronic myelogenous and 50 cases of chronic lymphatic leukemia—in many over a long period of time. These elements have been observed also in 35 cases of acute leukemia. Cases of true aleukemic lymphatic leukemia are not included. It has been possible to deduce from the accumulated observations certain conclusions regarding the platelets in these diseases so that this brief report is made.

Particularly complete and frequent observations of the formed elements of the blood were made on 35 of the patients with chronic myelogenous and 16 of those with chronic lymphatic leukemia. In

* Not only have the authors themselves made many of the determinations, but acknowledge with gratitude those made by Drs. A. H. Gunderson, L. Stern, and Miss Geneva A. Daland.

these cases of chronic leukemia blood examinations were made, as a rule, over a period of about three years, but on many the study extended over a much longer time, and in some throughout the entire course of the disease. Repeated doses of radium emanations or roentgen-rays were administered to these patients and to most of the others. There are at hand sufficient observations on the blood platelets of cases untreated and on patients at times remote from exposure to irradiation to warrant certain conclusions relative to the level of the blood platelets irrespective of treatment. For the purpose of determining the influence of the irradiation on the platelets there are many recorded observations. The immediate effects of irradiation, such as occur in the course of a few days, are not reported here. It is the more remote effects that are referred to below.

About a thousand counts of the blood platelets were made, using particularly the method of Wright and Kinnicut.[3] In cases in which the influence of irradiation treatment on the platelet count was studied the enumerations were checked often by simultaneous counts made both with Pratt's[4] and Buckman and Hallisey's[5] method. Thomsen's[6] technic was used occasionally, but not simultaneously with the others. These different methods yielded substantially the same results, though Thomsen's method perhaps tended to give the highest figures. Besides actual counts, estimates of the level of the blood platelets, based on inspection of properly prepared and stained blood films, yielded much data and serviceable information. There is ample justification for this procedure, as after a little experience close correlation between actual counts and estimations can be obtained, and were obtained in these cases of leukemia.

The Blood Platelets in Chronic Myelogenous Leukemia. The blood platelets in chronic myelogenous leukemia may be normal in number, increased or diminished, and in the same individual may vary markedly from time to time. However, in general, a given case shows a tendency to maintain throughout the greater part of the disease a definite level of platelets, be this within the normal or above or below the normal limits for the numbers of platelets in the peripheral blood (200,000 to 400,000 per c.mm.).

The data show that the differences in the level of the platelets in patients treated with radium or roentgen-rays are to be found in cases not receiving such treatment. Likewise changes in the numbers of these elements in a given case occur independently of irradiation, just as similar fluctuations occur in the numbers and characters of the red and white cells. However, irradiation affects the platelets and frequently can bring about desirable changes in their numbers and character, just as it alters favorably the occurrence in the blood stream of the other blood corpuscles. Irradiation may be responsible for a decrease of platelets to an undesirably

low level—by itself a sign that is important to recognize and one that necessitates caution regarding further treatment.

As a rule, we have found the platelets to be normal or slightly increased early in the disease, but marked changes in their numbers nearly always occur before death. Complete data on 35 cases irradiated at various intervals show that 26 had from a normal to a somewhat increased number of platelets (700,000 per c.mm.) during most of their illness. In nearly all there were periods of short duration, seldom over six weeks, when the platelets became much more increased above normal, while a few cases showed a transient decrease. The platelets persistently became decreased, below normal in 21 cases, beginning usually about three months, but varying from eight months to two weeks, before death. In 7 of these patients the decrease was extreme (below 50,000 per c.mm.) usually for about the last two months of life. In 3 of the 26 cases, which during most of their disease had a slightly increased number of platelets, these elements appeared in excessive numbers for a few months before death. There were 7 of the 35 patients who persistently showed during most of the course of the disease an excessive number of platelets (800,000 to 2,000,000 per c.mm.). In but 1 of these did the platelets fall to a number below normal and then in the last month of life. In some death followed a persistent rise of the platelets to enormous numbers, while in others these elements showed a tendency to fall before death, though their numbers remained well above normal. In only 2 cases did the platelets remain below normal during between 50 and 75 per cent of the course of the disease. In neither did the number of these elements ever even temporarily rise above normal, while in both the platelets decreased still more, and remained exceedingly sparse in the last two months of life.

Within rather wide limits the actual level of the platelets maintained in a given case, provided they are not very few, is of relatively little importance in forecasting the prognosis. Marked changes from this level, particularly when not transient, yield significant information. In spite of the fact that the megacaryocytes are involved in the morbid process, their frequent presence in the peripheral blood, as well as marked variations in the numbers and characters of their derivatives, the platelets may be and often are affected independently of the other narrow elements. The level of the platelets is not necessarily controlled by the status of the white cells or red cells and marked changes in the level of platelets may occur without involving the other two marrow elements. When a case first comes for irradiation treatment the white cell count is usually high and the platelets may be very few or normal and less often considerably increased. It is true, however, that when a high percentage of immature cells is present the platelets are apt to be few. It is likewise true that when the white cells

show many atypical or abortive forms, such as are prone to occur with advancement of the disease, the number of platelets is usually abnormal. Whenever there occurs through the intervention of treatment or otherwise a rise of the platelets from a definitely subnormal number, or a fall from an excessively high level to an essentially normal one, there follows clinical improvement in the patient provided the character of the leukocytes is altered in the direction of a normal blood picture. It was not unusual to see among the cases which were studied, that those with marked thrombopenia and high white cell counts soon after irradiation had flooded the peripheral blood with excessive numbers of platelets which within a few weeks fell toward normal. A shift in the platelet level toward normal values was not, however, a *sine qua non* of improvement, inasmuch as 4 cases with excessive numbers of platelets and 1 with a constant slight diminution of these elements frequently showed clinical improvement as well as a more nearly normal white cell picture, without important changes in the platelet count. A decline in the platelet count to a markedly subnormal value that was not soon restored by Nature or irradiation often preceded by not many months a fatal outcome. The temporary spontaneous decreases observed were apt to be associated with other undesirable features of the blood. A transient marked increase of platelets, not related to irradiation, exhibited by patients who usually showed a normal or slightly increased number of platelets, was apt to forecast undesirable departures from normal in the other blood elements.

An increasing number of immature white cells denotes that untoward symptoms will soon appear and that the patient's basal metabolic rate will rise. Changes in the red cells and blood platelets also may be indicative of this increased activity of the disease process. As relapse develops, the alterations in the platelets will occasionally quite overshadow those of the other blood elements. They may rise markedly and present much diversity in character, and their parent cells appear in the blood in unusual numbers. Such a picture carries the same significance as increase in immature white cells and irradiation can restore the megacaryocyte elements to normal. Under such circumstances, if irradiation is not given soon, the white cells and later the red cells will present an increasingly and markedly abnormal picture.

It is evident that a marked deviation of the platelets away from normal numbers is a bad prognostic omen. One may assume that some unknown agent in one amount stimulates the megacaryocytes and in other amounts paralyzes their functions. A marked increase of platelets is associated undoubtedly with the sharing of their parent cells in the morbid process. Though unusually high levels of platelets are to be found rather persistently in some cases while they continue in fair health, such patients will not be found to

remain so well as comparable cases with similar blood pictures, but with a more normal number of platelets. Likewise the chances for a long course of the disease become less favorable in patients with a persistently distinctly high platelet count than in those whose platelets approximate normal numbers. When extraordinary numbers flood the blood, except perhaps for very short periods of time, it indicates an impending state of affairs that is relatively serious.

Decrease of the platelets to markedly low levels is more serious than a marked increase, especially if they do not soon rise and if the total white cell count is relatively low. The thrombopenia which is often seen when many of the nucleated cells are of a character associated with a greatly increased activity of the leukemic process, for example, a high percentage of myeloblasts may be brought about by a rapid growth of immature white cells inhibiting the development of the megacaryocytes. Rarely in myelogenous leukemia a decrease of platelets is dependent upon an actual marrow aplasia. A permanent and marked alteration from the platelet level constantly shown by our patients, particularly when accompanied by increased numbers of abnormal white cells portended a relapse, which was followed usually by death in six months or less. Conversely it was generally, but not invariably, true that until such a change did take place the outlook was good for the immediate future of the patient.

Improvement in the patient's condition derived from irradiation[7] is reflected in the blood picture. By far the most important information is to be gained from a study of the white cells, which always show changes toward normal after beneficial treatments. In an effort to obtain the maximum knowledge neither the red cells nor the platelets are to be neglected. The number of platelets, if changed markedly in the direction of normal, is a sign that is followed usually by a better state of the patient's health. On the other hand remission may occur without important changes in the numbers of platelets, while these elements, particularly after repeated irradiation, may be altered in the direction of normal without clinical improvement. However, a definite shift in the level of platelets toward normal, coincident with improvement of the white cell picture, constitutes additional evidence of effective treatment. Under such circumstances a more pronounced or longer remission is to be expected than if no change in a distinctly abnormal platelet count had occurred, or if the change had occurred for more than a short period in a direction away from normal.

The Blood Platelets in Chronic Lymphatic Leukemia. Decrease of the blood platelets is a characteristic feature of chronic lymphatic leukemia, believed to result from a crowding out of their parent cells in the marrow by the lymphocytic cells. The degree of their decrease, like the decrease of hemoglobin and red cells, serves to indicate the amount of marrow insufficiency which becomes more

marked as the disease progresses or becomes more acute. About half of 50 cases when first seen showed a distinct diminution of platelets; in the others they were within normal limits, but usually near the lower normal limits. In only 2 were they slightly above normal (550,000 per c.mm.). This patient and those with the more nearly normal number of platelets had suffered from the disease a shorter time and lived on the average distinctly longer after they were first seen than those with decreased numbers of platelets. In all of the 50 cases studied, including 16 upon whom platelet counts were made very frequently, marked thrombopenia sooner or later occurred, and there was no particular tendency in any given case to maintain a fixed platelet level. Marked reduction of these elements occurred whenever the total number of lymphocytes was excessive (over 175,000 per c.mm.), the percentage of immature forms high (over 30 per cent) or the hemoglobin level low (below 60 per cent). Whenever a few bone-marrow white cells occurred in the blood, which is the rule as the disease advances, because the bone-marrow elements become crowded out by lymphocytic foci, the platelets in turn are affected and usually fall below previous levels. There was observed no further correlation between the numbers of platelets and the blood elements.

In many cases with only a moderate diminution of platelets there occurred a rise, nearly always slight, simultaneously with reduction in the number of lymphocytes and clinical improvement. This took place both spontaneously and following irradiation. However, such improvement frequently occurred in the face of a continued sparseness of platelets, but was apt to be of a slightly less satisfactory character than when the platelets increased. In no instance did the platelets fluctuate from very low numbers to above normal and rarely even to normal, as they do in myelogenous leukemia. At times for some weeks following irradiation a rise of platelets from a level of about 175,000 per c.mm. to a little above normal occurred and this always forecasted a good state of the patient's health for at least some months. Marked thrombopenia, though always present at death, often persisted for a long time before the termination of the disease, and therefore thrombopenia cannot be taken to indicate as in chronic myelogenous leukemia a relatively rapid decline to a fatal outcome. On the other hand, a relatively rapid change to a very low level of the platelets occasionally took place, followed soon by death.

Following irradiation it generally happens that no significant rise in the platelets occurs, even when the white cell picture and the clinical condition of the patient improve. Irradiation can depress platelet formation, and in these patients, who already have a decreased activity of megacaryocytes, one must realize that this therapy can and often does suppress their functions further, leading to undesirable results. It was common in advanced cases,

especially with low white cell counts (below 30,000 per c.mm.), to observe that irradiation further decreased the platelets. When irradiation was given in the presence of marked thrombopenia significant improvement was unusual. This is in contrast to the fact that in untreated cases of myelogenous leukemia under similar circumstances improvement is usual and the platelets rise, perhaps suggesting a difference in the character of the cause of the platelet deficiency. The readily produced untoward influence of radium or roentgen-rays on the platelets in lymphatic leukemia demands that these elements be watched carefully in order to prevent, from too much treatment, more marrow depression than already exists. In general, a knowledge of the platelet count in this disease is helpful in diagnosis, in prognosis and in estimating the extent to which useful irradiation therapy can be given. All cases with a normal number of blood platelets will be found in good condition, and an increase over previous levels is a most desirable finding. However, it is surprising how often these elements may be decreased to a considerable extent without the patients being particularly ill or exhibiting purpura.

The Blood Platelets in Acute Leukemia. In both forms of true acute leukemia, from at least as soon as symptoms are evident and until death, decrease of the platelets is found always and becomes extreme, as is usually the case in acute phases of chronic leukemia. Irradiation may cause a rapid further decline. Whether, perchance, very early in acute myelogenous leukemia the platelets may be increased is unknown. That this may be true is suggested by the fact that in 5 cases of atypical subacute myelogenous leukemia, which had had their illness on the average for ten months, the platelets were somewhat increased and most abnormal in character with megacaryocytes present, although thrombopenia developed as death approached. These patients had no remissions and were not affected in any important way by irradiation. They had only slight splenic enlargement, bone pain was prominent and their white cells numbered usually about 25,000 per c.mm., composed chiefly of very immature cells.

The Relation Between the Blood-platelet Level and the Occurrence of Hemorrhage in Leukemia. It is well recognized that in the symptomatic state of purpura hemorrhagica (thrombopenic purpura) there is a marked diminution of the platelets, but that all symptomatic hemorrhagic conditions are not related to this defect. In about 50 per cent of our cases of chronic myelogenous leukemia, for whom records of the whole course of the illness are complete, there developed petechiæ, sometimes with other purpuric lesions. The petechiæ were often few, but occasionally coincident external or internal hemorrhages occurred with a continued paucity of platelets. The purpuric manifestations usually appeared toward the close of the patient's illness. In some cases the symptom was

evident a few years before death and disappeared as the platelets rose after irradiation. Hemorrhages also occur in this disease when the platelets are normal as well as when they are much increased (1,500,000 per c.mm.). Under such conditions it is to be emphasized that petechiæ have not been seen, but rather bleeding in the form of ecchymoses from trivial trauma, epistaxis, and bleeding from a surgical operation, such as removal of a tooth. Such blood loss occurred in about 25 per cent of the cases and apparently always at a time when deviations from normal in the white cell picture were marked. Similar hemorrhages occur in erythremia and are considered related to the altered physical state of the polycythemic blood. A comparable condition due to the leukocyte increase probably exists in leukemia. Hemorrhage in chronic myelogenous leukemia may result also from the leukemic infiltration of different organs; for example, the kidneys, leading alone or when combined with the effect of a low platelet count to hematuria, usually slight, as occurred in 15 per cent of 110 cases.[8]

In chronic lymphatic leukemia purpura in the form of petechiæ and ecchymoses is observed much more frequently, usually more extensively and for a much longer time than in chronic myelogenous leukemia. This is to be expected because thrombopenia is a feature of the disease throughout a great part of its course. Bleeding from mucosæ and into organs is not uncommon. The hemorrhagic manifestations of thrombopenia are present nearly always a few weeks, rarely for but a few days, before death. Nevertheless petechiæ and ecchymoses in varying amounts are seen quite often during many months and even as long as two years before the termination of the disease. We have seen a few cases that have had purpura for many years before signs of leukemia became obvious. The purpuric lesions were present a year before death in at least 10 per cent of 80 cases which had had their disease, on the average, for 3.45 years.[9] When irradiation is given in the presence of outstanding purpura, always occurring in this disease with profound thrombopenia, symptomatic benefit is very unusual, quite in contrast to the results observed in chronic myelogenous leukemia. In spite of the frequency of a decrease of platelets in chronic lymphatic leukemia, many cases exhibited no purpura when the platelet count had fallen and remained below a level (60,000 per c.mm.) at which purpura usually is expected, though it developed sooner or later as death approached. In fact, one of the striking and unexplained relationships between the numbers of platelets and spontaneous bleeding is that their actual decrease does not indicate the amount of hemorrhage in different cases or in the same case at different times. Hemorrhages never occurred in the cases of lymphatic leukemia when the platelets were normal in numbers. Blood loss due wholly or partially to leukemic infiltration does occur in lymphatic as in myelogenous leukemia.

In acute leukemia it is the rule that all the manifestations of symptomatic purpura hemorrhagica develop, and often to an intense and distressing degree.

Summary. A study of the blood platelets yields useful knowledge for guiding treatment and appraising the state of health of a patient with leukemia. In chronic myelogenous leukemia the numbers of these elements may be normal, enormously increased, or greatly diminished, and in chronic lymphatic and acute leukemia it is the rule to find them below normal. The fluctuations that occur in the numbers of blood platelets are discussed. Petechiæ and other hemorrhages associated with decrease of blood platelets are common, and hemorrhages, but not petechiæ, may occur in chronic myelogenous leukemia when the platelets are much increased.

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A SUMMARY OF THE EFFECTS OF EXTERNAL HEAT UPON THE HUMAN BODY.

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The application of external heat to the human body constitutes one of the oldest forms of treatment of which there is any record. Heat was used extensively by the ancients in the form of hydrotherapy and has since been widely applied as hydrotherapy alone or in such accessory forms as hot-mud baths, turkish baths, hot packs, vapor baths, hot-air baths and electric-cabinet sweats. It has been increasingly applied to a large variety of diseases.

Although the undoubted benefits from the use of external heat have long been recognized, but little attempt has been made to understand the *modus operandi* of the processes concerned. The therapeutic application of heat has, for the most part, been left to uncritical observers, and it is common knowledge among the laity as well as the profession that damage as well as benefit often accrues, probably as the result of misapplication and undue zeal. There are

in this country and Europe establishments whose employment of these measures is not highly discriminating, although at the better-known resorts the supervision of a physician is required.

It has therefore long been important to ascertain what transpires during exposure of the body to external heat, with the double aim of learning something of the pathology underlying conditions thus influenced for the better and also of determining the limitations and dangers in the methods themselves. The past three or four years have been productive of data of value which, however, are scattered through journals not necessarily widely read by the general medical public. It is chiefly to the general medical public however, that the information recently acquired is of value, and it is therefore the purpose of this article to endeavor to correlate the various lines of work on the subject and to state briefly the changes that occur so far as our knowledge permits.

In conjunction with his associates, the writer has for some years been studying the changes accruing from exposure of the body to external heat in the form of radiation from electric lamps, the so-called "bake." Within limits, the principle involved is much the same whatever be the source of the heat, and the electric cabinet bake lends itself to study more readily than do other and more cumbersome processes, some of which require elaborate equipment. Bazett and Haldane[1] showed that subjects immersed in water at a temperature of 38° C. experience a rise in the body temperature, accompanied by hyperpnea, sometimes a sensation of giddiness, a fall in the alveolar carbon dioxide and an alkaline sweat. Haggard,[2] in experimenting upon himself in a bath at 40° C. for twenty minutes, observed similar changes in the alveolar air, together with a drop in the CO_2 content of the blood. As he observed no fall in the carbon-dioxide combining power he postulated a lowering of the hydrogen-ion concentration of the blood.

Pemberton, Hendrix and Crouter[3] observed an analogous fall in the alveolar CO_2 during exposure of the body to an electric cabinet bake, with a rise in the CO_2 after the bake. The same writers also conducted a series of observations upon the oxygen content and capacity of the venous blood, and found that during the course of an electric bake the oxygen content rises very appreciably although the capacity is but little altered. This rise in the percentage saturation of the blood with oxygen is presumably due to the increased rate of bloodflow.

The phenomenon of sweating which accompanies these measures has been regarded as perhaps the chief desideratum and certainly one of the criteria of successful administration of this form of therapy. In general, the benefit arising from sweating has been ascribed to an elimination of nitrogenous substances and possibly salts. This conception undoubtedly finds support in cases of nephritis where the blood nitrogen is high and removal of part of

it through the sweat in the form of urea can be demonstrated. This explanation, however, has been assumed as adequate in other conditions where the nitrogenous elements of the blood are not concerned. Medical literature is full of references to the "elimination" achieved by these measures, but there have been few suggestions and fewer data to indicate what the substances eliminated might be.

It has long been recognized that carbon dioxide is eliminated to some degree in the sweat. Thus, at a temperature between 29° C. and 33° C. the CO_2 output is about 35 gm. per hour, but when the external temperature rises above 33° C. the output increases; at 34° C. it may be doubled and at 38.5° C. it may be more than trebled (Starling[4]). There is a paucity of data in the literature upon sweat, however, and the changes which it undergoes, if any, during exposure of the body to heat. The data bearing upon the reaction of the sweat have been contradictory, and Pemberton and Crouter[5] undertook a study of the hydrogen-ion concentration of the sweat during electric bakes. It was observed that the sweat under these circumstances in normal individuals has an average initial reaction or pH of 7, which is very slightly on the acid side of the blood reaction, although there may be departures either way. The first sweat to appear may thus be acid, alkaline or neutral, but whatever the initial reaction, it invariably undergoes a change towards the less acid or more alkaline range which continues progressively during the course of the bake, generally becoming markedly alkaline. The only exceptions to this so far observed have occurred in a few cases of arthritis and one of scleroderma whose sweat tended to remain very acid throughout—around 4.6.

It was at first thought that the change in the reaction of the sweat might be referable to a lower acidity brought about in it by loss of carbon dioxide from it, especially as it was found that the carbon-dioxide content of the air in a rubber bag placed around the arm increased more or less parallel with the drop in acidity of the sweat elsewhere. Further observations by Cajori, Crouter and Pemberton[6] showed that this apparently is not the mechanism concerned. On determining the so-called carbon-dioxide absorption curves of the blood before and during the bake it was discovered that there is a change in their level, a rise, which means that as the bake progresses the blood is able to absorb more carbon dioxide. More alkali becomes available, or, in other words, the blood becomes more alkaline. Following this change the urine generally becomes more alkaline also. These observations were further controlled by studying the hydrogen-ion concentration of the blood directly by means of Cullen's colorimetric method and comparable results were obtained, the hydrogen-ion concentration or acidity decreasing. Since the completion of these studies Koehler[7] has published analogous changes during the hyperpyrexia of

fever and also as the result of a rise in body temperature following extremely hot baths. He measured the pH of the blood electrometrically by means of the calomel electrode so that in principle the same results have been arrived at by several methods and different observers.

It therefore appears that during the therapeutic application of external heat, not to mention the more severe applications which most of the above workers employed, there occurs a loss of acid from the body which results in a relatively increased alkalinity of the fluid tissues. This acid is mainly CO_2 and it makes its escape chiefly through the lungs, although there is also a considerable output through the urine,[8] and also through the sweat as above described. Other acids are also eliminated, and Cajori, Crouter and Pemberton[9] have shown that in the sweat lactic acid is one of them, although the total amount is not great. The result of this loss of acid from the body is that the blood becomes relatively more alkaline, and in order to maintain its equilibrium it eliminates the excess alkali through the urine and sweat.

It is, therefore to be appreciated that very profound changes in the acid-base equilibrium of the blood follow even what has been regarded as a mild therapeutic measure. The change in the reaction of the blood was in one case from a pH of 7.26 to 7.52. It is not surprising, therefore, that so many undesirable consequences have followed the use of hydrotherapy and external heat when these measures are carried out in a wholesale way. In addition to the change in the blood reaction, which must be resisted and compensated for, there is the previously recognized rise in the general metabolism from the increased bloodflow, and Gram[10] has recently shown by observations on the hemoglobin that the blood becomes more concentrated. The full consequences of alkalosis are not entirely known, but one of the baneful effects is the induction of tetany.

It is believed that the general nature of the above reaction should be understood by all persons who concern themselves with the application of external heat to the human body in order that there may be a more intelligent appreciation of what is to be accomplished and of the possible dangers. As a corollary to the above, it is interesting to note that the benefit of hot packs and sweats in nephritis may be due not solely to the elimination of nitrogenous substances, as so long believed, but also, in part at least, to the relative alkalosis brought about by the elimination of acid radicals, chiefly CO_2. The influence of these processes upon the acidosis of nephritis or other conditions is obvious.

Summary. Exposure of the body to the therapeutic application of external heat results in a heightened bloodflow, an increased metabolism and in the elimination of acids, chiefly carbon dioxide which escapes through the lungs, urine and sweat in the order of

magnitude named. This leaves an excess of alkali in the blood which then changes its reaction, becoming more alkaline. In the compensatory effort to meet this situation, the excess of alkali is eliminated through the sweat and urine. The profound nature of the changes induced by these measures is clearly indicated, and explanation is afforded of some of the baneful consequences which follow their uncritical use. If carried to extremes tetany may result. The available evidence indicates that part of the benefit of the sweat process in some forms of nephritis is due to loss of acid substances from the body, with consequent benefit to the acidosis frequently accompanying renal disease.*

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DYSTROPHIA ADIPOSOGENITALIS, WITH ATYPICAL RETINITIS PIGMENTOSA AND MENTAL DEFICIENCY—THE LAURENCE-BIEDL SYNDROME.

A Report of Four Cases in One Family.

By Solomon Solis-Cohen, M.D.,

and

Edward Weiss, M.D.

PHILADELPHIA.

The purpose of this report is: (1) To place on record the histories of four members of one family who present overgrowth of fatty tissue and undergrowth of the genitalia—the so-called Froehlich syndrome—associated with other abnormalities of development, including retinal atrophy with pigmentary filtration; (2) to call attention to previous reports of cases so closely parallel to ours, that we may, with Biedl and Raab, look upon the condition as a definite syndrome.

Catherine L., a girl of Italian parentage, aged seventeen years, was admitted to the medical ward of the Jefferson Hospital, Octo-

* The work of the writer and his associates constitutes part of a study on arthritis in collaboration with Robert B. Osgood, Boston.

ber 22, 1923. She was delirious and had a high fever. The cause of this was determined to be acute pyelitis. Her temperature soon became normal, but after a few days rose again, and again subsided; and thus during November and December she continued to have flights of fever lasting for several days. Finally, shortly after the New Year, her temperature remained constantly normal, all evidences of pyelitis having disappeared. During the period of this illness we had noted with interest the girl's strange appearance, odd behavior and remarkably poor vision; and during an afebrile interval had had her eye-grounds examined by one of our colleagues (Dr. Heed), who recognized the condition present; but not until the acute infection had entirely subsided, did we deem it opportune to make a thorough study.

Questioned concerning her family, Catherine informed us that there were 8 children; 3 others, like herself, fat and with poor vision; 4 thin, and with good vision. The 7 were brought to the dispensary and studied; the father and mother were seen at their home. The photographs of the affected children are reproduced in Figs. 1, 2, 3 and 4.

The father, a day laborer, aged sixty years, was born in Italy, about 100 miles north of Rome, in a healthy district where no endemic disease prevails. He was the first born of a family of 6, 4 boys and 2 girls, all of whom are living and well. Neither he nor his brothers, sisters, or parents, suffered from known visual defect. None has exhibited marked adiposity, polydactylism, deafness or idiocy; nor, insofar as he could inform us, were these phenomena present in other relatives. This, however, may indicate merely ignorance of family ramifications, or the peasant's failure to take notice, and does not necessarily imply absence of such dystrophies in previous generations, or in collateral lines.

The same holds true as to the mother, who is fifty-two years of age, and has no known kinship with her husband. She was born in the same district in Italy (the Abruzzi); was fifth in a family of 6, 1 boy and 5 girls. She married when twenty-one years of age, and in addition to her 8 living children had 1 miscarriage. This occurred without known provocation, in the second or third month of her second pregnancy. Both father and mother have always been healthy, and in both the blood Wassermann reaction is negative. Of their 8 children 4 are abnormal, as indicated in the following list:

Male, aged twenty-five years, normal.
Male, aged twenty-one years, *abnormal.*
Female, aged nineteen years, normal.
Female, aged seventeen years, *abnormal.*
Female, aged fifteen years, *abnormal.*
Female, aged thirteen years, normal.
Male, aged eleven years, *abnormal.*
Female, aged nine years, normal.

We might add, as to the last named, that, both physically and mentally, she is uncommonly alert, acting as shepherdess to the abnormal flock on their visits to the hospital.

Detailed description of the affected members of the family follows:

Case Reports. CASE I.—Catherine (Fig. 1), the child who first engaged our attention, had a normal birth and seemed a fat, normal infant, except for six toes on the right foot, one of which was later amputated. Dentition began at the fifth or sixth month; she began to walk at one year and to talk at two years. She had measles and

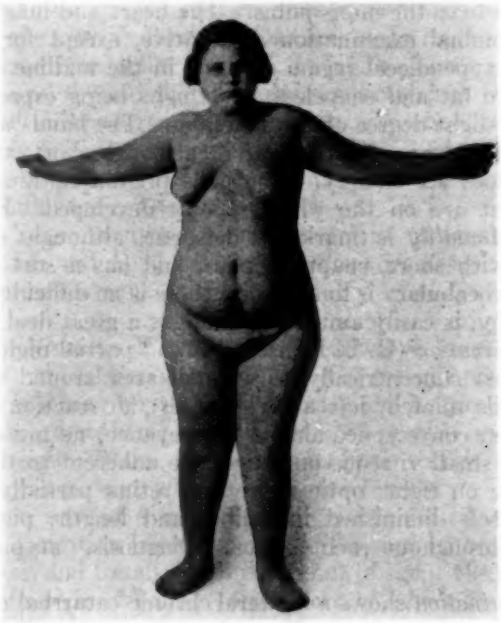

FIG. 1

whooping-cough, from which she made good recovery. Diminution of vision became noticeable at about the age of fifteen years, and has been progressive since. She did not menstruate until she was about seventeen years of age (May, 1923), and then not again for nine months. One month prior to her admission to the medical service she had been brought to the hospital with a diagnosis of acute appendicitis, but at operation an ovarian cyst, with twisted pedicle, was discovered.

Physical examination in the medical ward, after she had recovered from the attack of pyelitis (January, 1924), showed a very stout, short girl, with high color and an ordinary amount of coarse

black hair. She weighed 152 pounds. Her height was 144 cm.; her span, 142 cm.; from symphysis to sole she measured 71 cm., and from symphysis to vertex, 74 cm. Her expression was staring, but not vacant. She found her way with difficulty, bumping into objects as she moved about.

The face is round, the nose small, the teeth normal, the palate high arched, the tonsils large and cryptic; the neck is short and chunky and the occiput is sheer. There is no adenopathy. The *thyroid gland* is palpable, but not enlarged. The breasts are large and pendulous. *Adiposity* is marked and generalized, but is especially of the mammary, mons and girdle type. The hair growth in the axilla and pelvic regions is scanty. It has the usual feminine distribution over the mons pubis. The heart and lungs seem normal. Abdominal examination is negative, except for two scars, one in the appendiceal region and one in the midline. The arms and legs are fat and shapeless, the thighs being especially thick. There is a slight degree of genu valgum. The hands and feet are short, thick and broad. The fingers, although short, are tapering, while the toes are chunky. The nails present nothing of special interest, but are on the whole, poorly developed. Reflexes are normal. *Mentality* is markedly deficient, although she answers questions with short, snappy replies, and has a sort of infantile wit. Her vocabulary is limited, but there is no difficulty in speech. She is happy, is easily amused and laughs a great deal.

Eye examination (H. F. Hansell) shows "partial night blindness; fields limited concentrically to a small area around the fixation point; pupils dilated, left a trifle larger; no reaction to light or convergence; convergence almost in abeyance; no muscular paralysis; a few small vitreous opacities, one adherent to the posterior lens surface on right; optic nerve and retina partially atrophied; retinal vessels diminished in caliber and length; pigment spots scattered throughout each fundus. Diagnosis, 'atypical retinitis pigmentosa.'"*

Ear examination shows a bilateral chronic catarrhal otitis media.

Laboratory examination: The urine output was about 1 liter in twenty-four hours; examination negative. Blood count shows: Hemoglobin, 57 per cent; red blood cells, 3,690,000; white blood

* In a report of these same patients, read before the Oxford Congress of Ophthalmology in July, 1924, by H. F. Hansell, he makes the suggestion that a better term than retinitis pigmentosa for this condition would be "optic nerve and retinal atrophy associated with pigment filtration," as being more nearly descriptive of the clinical and pathological process. W. H. Wilmer (Arch. Neurol. and Psychiat., 1924, **12**, 137), in a paper entitled "Hereditary Factors in Optic Atrophy and Retinitis Pigmentosa" suggests the term "pigmentary degeneration of the retina;" or would accept Collins's suggestion of "abiotrophy of the retinal neuro-epithelium," perhaps simplified as "retinal abiotrophy." ("Abiotrophy," a term introduced by Gowers, is defined by Collins as "The premature failure of the inherent vitality of a tissue, giving rise to impairment or destruction of certain functions before the death of the organism as a whole.")

cells, 10,000; differential count normal. Blood-pressure averaged 110/70. Blood Wassermann was negative. Basal metabolism was −19. Sugar-tolerance tests showed a deficient response to the ingestion of 1.75 gm. of glucose per 1 kg. of body weight.

Gynecological examination shows external genitalia normal, except for the sparse growth of pubic hair. Examination of the internal genitalia discloses an infantile uterus.

Roentgen-ray study fails to demonstrate the presence of the thymus gland, nor does it show any changes in the long bones or their epiphyses, or the bones of the hand or wrist. The sella turcica was reported as "within normal limits in size." The dorsum is perhaps somewhat higher than common. Our general observation however, and the careful studies of Schaeffer and de Schweinitz reported in the latter's Bowman Lecture, make us chary of drawing conclusions from sellar shadows.

Pituitary and thyroid therapy produced no change in weight, in mentality or in temperament. The girl said she "saw better," but there was no objective confirmation of this, and suggestion was not absent. Moreover, there was hospital care and rest as a general upbuilding influence. The menses appeared for four days in February, 1924 (nine months after the previous menstruation), and again in March and April. This seemed, at least, to be the result of the endocrine therapy.

CASE II.—Nicholas (Fig. 2), aged twenty-one years, the oldest of the abnormal children, is very much like the girl just described. He is a big laughing boy, with high color and a sparse growth of hair in the beard region. He weighed 221½ pounds and measured 160 cm. in height; 78 cm. from the symphysis to sole, and 88 cm. from symphysis to vertex. His span was 159 cm.

At birth he seemed a normal child, except for six toes on the right foot. Dentition began at six months, and he began to walk when one year, and to talk when two years, of age. He had measles and scarlet fever in childhood, from both of which he made good recovery, and he has not been sick in bed since. He says, and his parents affirm, that he has been fat all his life. At the age of sixteen years he noticed some failure of sight, and this has grown progressively worse. He works as a newsboy at night, making his way to and from his stand with great difficulty, on account of his poor vision. Otherwise he is in excellent health.

Physical examination reveals *adiposity* chiefly of the mammary, mons and girdle type. He has some degree of genuvalgum. His hair is black, coarse and thick. The eyes are almost constantly moving, the nose is small, the ears are thick and set close to the head, the teeth are good, the palate is high arched and the tonsils are large. The back of the head is straight with the neck, which is short and thick. The *thyroid gland* is palpable, but not enlarged.

The heart and lungs are normal; abdominal examination is negative. The axillary hair is rather sparse; pubic hair is about normal in amount and distribution. The *penis* is very small; the testes, however, seem normal in size. The hands and feet are broad and thick. There is no adenopathy, and the reflexes are normal. He, too is *mentally* deficient, but seems more intelligent than his sister. He counts in "twos," probably because his papers sell for two cents each. He is of a very merry disposition, is easily amused and laughs readily.

FIG. 2

The *eye report* is as follows: "Highly myopic and astigmatic; night blindness, increasing each year. There is a rapid, jerky vertical and rotary nystagmus, augmented by attempts to see objects held close to the eyes. The optic nerves are atrophic; the arteries and veins are reduced markedly in size. Pigment spots and a few 'bone corpuscles' are scattered throughout the fundi. The fields are limited to a small area around the fixation point. Convergence is deficient. Pupils are equal and react." (Hansell).

Laboratory studies are as indicated in the accompanying chart which gives the principal data of our records arranged in tabular form. Basal metabolism was normal; sugar tolerance slightly reduced.

TABULATION OF THE PRINCIPAL DATA OF OUR RECORDS.

	Nicholas, 21 yrs.	Catherine, 17 yrs.	Anna, 15 yrs.	Joseph, 11 yrs.
Dentition	5–6 mos.	5–6 mos.	6–7 mos.	6–7 mos.
Walking	12 mos.	12 mos.	16 mos.	11 mos.
Talking	2 yrs.	1½ yrs.	2 yrs.	15 mos.
Poor vision noticed	16 yrs.	15 yrs.	13 yrs.	10 yrs.
Present weight, pounds	221½	152	121	110
Height, cm.	160	144	136	136.5
Span, cm.	159	142	138½	129
Symphysis to sole, cm.	78	70	67	65
Symphysis to vertex, cm.	82	74	69	71.5
Temperature, pulse and respiration	Normal	Normal	Normal	Normal
Urinalysis	Negative	Negative	Negative	Negative
24-hr. output, in cc	900–1000	1000	800	1000
Blood-pressure	130/90	110/70	120/85	110/60
Blood count	Normal	Secondary anemia	Normal	Normal
Wassermann	Negative	Negative	Negative	Negative
Basal metabolism	−3	−19	−29	−21
Sugar tolerance 1.75 gm. per kilo body weight (per cent, blood sugar):				
Before	0.118	0.098	0.116	0.101
½ hour	0.246	0.176	...	0.166
1 hour	0.268	0.199	0.190	0.125
2 hours	0.163	0.202	0.135	0.109

Roentgen-ray studies show normal long bones, wrist and hand; the sella turcica is reported as "slightly smaller than the average." The posterior clinoid is high. No thymus shadow can be made out.

Endocrine therapy, pituitary and thyroid, over a period of eight months, has had no apparent effect on this boy.

CASE III (Fig. 3).—Anna, aged fifteen years, is a dull-looking, shy girl, excessively developed for her age. She weighed 121 pounds. She measured 136 cm. in height, 67 cm. from symphysis to sole and 69 cm. from symphysis to vertex; her span was 138½ cm.

She appeared to be a normal child at birth. Unlike the two whose histories have been detailed, she did not have an extra toe. Dentition occurred normally; walking and talking were somewhat delayed. She had measles, but made a good recovery, and has had no other illness. Her general health has been excellent. Dimness of vision was first discovered at about the age of thirteen years; it was noticed in school that she could not follow a straight line in writing. Menstruation began when fourteen years of age, and has always been regular.

Physical examination: Her *adiposity* is of the girdle, mons and mammary type; the mammæ are especially large. Her hair is straight, black and coarse; the teeth are normal; the palate is high and narrow; the tonsils are large. The *thyroid gland* is palpable, but not enlarged. Heart and lungs are normal; there is no adenopathy, and the reflexes are normal. The external *genitalia* are normal, but rectal examination discloses an infantile uterus. This

child, too, is deficient *mentally*, but does not seem to share in the exceptionally happy disposition shown by Nicholas and Catherine. Allowing for her mental hebetude, however, her mirth reactions seem about normal.

Roentgen-ray study of the sella turcica shows "floor rather uneven and posterior clinoid process inclined slightly backward." No thymus shadow can be made out. Roentgen-ray of the long bones, wrist and hand is normal.

Laboratory examination: A sugar-tolerance test showed a slight deficiency in her ability to handle glucose. The basal metabolism was −29.

FIG. 3

The *eye report* shows: "Media clear; numerous round, pigmented spots throughout the peripheral retina. The nerve is of fairly good color; the vessels are contracted. There is partial optic nerve and retinal atrophy. The fields are concentrically contracted Diagnosis, early retinitis pigmentosa." (Hansell.)

Hormone therapy seemed without effect on this girl.

CASE IV (Fig. 4).—Joseph, aged eleven years, the youngest of the abnormal children, is a dull-looking, fat boy, very much like the others. He weighed 110 pounds. He measured 136 cm. in height; his span was 129 cm.; from symphysis to sole he measured 65 cm., and from symphysis to vertex 71½ cm.

He was apparently a normal infant (no extra toes or other stigmata); dentition, walking and talking occurred at the common times. He had diphtheria at the age of ten years, and made a good recovery. Otherwise he has always been in good health. His dimness of vision, like his sister Anna's, became noticeable in school about one year ago, when he experienced considerable difficulty in reading and writing. Like Anna, he is *mentally* deficient, without marked euphoria.

FIG. 4

Physical examination shows an obese boy, with *adiposity* a little more marked in the girdle, mons and mammary regions. Like the other children, he has a high-arched palate and enlarged tonsils. His hands and feet are thick and chubby. *Genital* development seems fair for a boy of his age. There is a moderate degree of phimosis.

Eye examination shows the following: "A decided optic nerve and retinal atrophy. There are a few pigmented spots scattered throughout the periphery of each fundus. No myopia; no nystagmus. Patient too stupid to take visual fields. Diagnosis, atypical retinitis pigmentosa." (Hansell.)

Roentgen-ray study of the sella turcica, thymus and bones revealed nothing abnormal.

In laboratory study, reaction to sugar-tolerance tests was normal; basal metabolism, −21.

Hormone therapy seemed without effect.

Summary of Cases. Four of 8 brothers and sisters of Italian parentage, exhibit marked adiposity with mental deficiency, genital dystrophy and diminution of vision. Two of the abnormal children show polydactylism. The eye-grounds (H. F. Hansell) show atypical retinitis pigmentosa. The fat distribution is largely of the girdle, mons and mammary type. An hypophyseal lesion cannot be proved. Roentgen-ray examinations of the sella region do not show conclusive changes. No anomaly of osseous development is found. Sugar-tolerance tests do not indicate pituitary disease. Basal metabolism was below normal in 3 of the children. Both parents and children gave negative Wassermann reactions. The thyroid glands are palpable and within ordinary limits of size and consistence. There is no lymphadenopathy, and no history of rickets.

Family history of marked adiposity, visual defect, polydactylism, deafness or idiocy could not be obtained. The four unaffected children seem entirely normal; one, indeed, is uncommonly bright and active. Hormone therapy (pituitary—thyroid) seems to correct amenorrhea in the older girl, but otherwise was without effect on any of the children. Subjective improvement in the sight of the elder girl may have been the result of hormone therapy, but may with equal probability be referred to suggestion, or to the general improvement of nutrition attending hospital care.

Review of Similar Cases. A survey of the literature of retinitis pigmentosa brought out the following remarkably similar group reported by J. Z. Laurence and R. C. Moon, in 1866, under the title, "Four Cases of Retinitis Pigmentosa Occurring in the Same Family, Accompanied by General Imperfections of Development."[1] These authors describe the case of Marian T., aged seven years, 3 feet 8 inches in height, a flat-featured, heavy looking child with light auburn hair and gray irides. Her sight had been defective for two years. There was night blindness and slight lateral oscillation of each eye, combined with a very imperfect power of fixation. Ophthalmological examination revealed retinitis pigmentosa.

No hereditary tendency could be traced, nor were the parents related by blood. There had been 10 children in all; 2 died in infancy, 1 of smallpox and the other of consumption. Both the father and mother were active, intelligent and well built, with no imperfection in sight. The following description of the children was given by the parents:

Richard, aged twenty-four years, a fine young man, healthy in every respect.

Arthur, aged twenty-two and a half years, also a fine young man, healthy in every respect.

Harry, aged twenty years, *afflicted*, and has bad sight.

Ferdinand, aged eighteen years, *afflicted*, and has bad sight.

Charles, aged fifteen years, *afflicted*, and has bad sight.

Edwin, aged thirteen years, healthy in every respect, and very sharp at learning.

Willie, aged nine years, healthy in every respect.

Marian, aged seven years, a very quiet, slow child, *afflicted* with bad sight.

To this, the authors of the report add their observations, which we give in abstract:

Harry, aged twenty years, is short for his age, measuring 5 feet 3½ inches. He walks with a slouching gait, "as if he were tipsy," and appears to have hardly sufficient power to drag his legs; there is rather deep depression between the scapulæ. The curve of the lumbar vertebræ, however, is very considerable, causing the trunk to be thrown forward from the hips and the buttocks to be more prominent than usual. The lower extremities are short and the muscles flabby. He has a stolid, heavy countenance, and appears to be rather obtuse and unintelligent. He answers question slowly, but with tolerable accuracy.

Eye examination shows the power of fixation imperfect and the eyes rather continuously moving from side to side. The eye-grounds show retinitis pigmentosa.

Ferdinand, aged eighteen years, is 4 feet 6½ inches tall. He is a fat, heavy-looking boy, and, like Harry, he walks with a slouching heavy gait, dragging his legs from the hips. Eye-sight was first noticed to be defective at the age of six or seven; it has become progressively worse ever since. Eye examination shows retinitis pigmentosa.

Charles, aged fifteen years, is 4 feet 4 inches tall. He is dull and and inanimate, and walks with a slouching gait, but not to the same extent as his two brothers. Sight has been defective since one year of age. Eye examination shows retinitis pigmentosa.

The organs of regeneration are also strikingly implicated in the general want of development. There are no signs of rickets, scrofula or syphilis.

We quote the closing paragraph of this noteworthy and philosophical report. (The italics are ours.)

"In calling these cases by the name of retinitis pigmentosa, we have been guided by usage rather than by the intimate nature of the cases. Had we taken the latter view, we would rather have entitled our paper, 'Four Cases of Arrest of Development and Atrophy of the Eye,' or we might even *have gone a step further in the generalization of our title, as the arrest of development was by no means confined to the eye*, but affected several other organs of the

body. In this latter point of view, and more especially when we regard the mental faculties, these patients may in a certain sense be *compared with cretins* in a mild degree. In no member of the entire family was there any bronchocele."

SUMMARY OF REMARKABLY SIMILAR FAMILY GROUP REPORTED BY LAURENCE AND MOON IN 1866. Four of 8 brothers and sisters of healthy parents, showed retinitis pigmentosa, adiposity, genital dystrophy and mental deficiency. Three of these likewise showed imperfections of bony and muscular development leading to defective gait. There was no sign of rickets, of scrofula or of syphilis. The authors recognized that the retinal changes were but part of a general developmental failure and that, especially in view of the mental condition, these persons could be, not inaptly, compared to cretins.

SIMILAR CASES RECOGNIZED AS A SYNDROME BY BIEDL. Raab, in the course of a very careful study from Biedl's Clinic, emphasizes the occurrence of "a syndrome, perhaps familial, hitherto scarcely known, of (1) optic atrophy with pigmentary degeneration similar to retinitis pigmentosa, (2) polydactylism, (3) obesity and (4) genital hypoplasia." Except for its failure to include mental deficiency, this description agrees with our cases, as well as with those cited from Laurence and Moon. Biedl, however, when in Philadelphia in the spring of 1924, saw our patients, and in confirming our opinion of the identity of the syndrome with that which he had described, included the mental phenomena. Indeed, he laid stress on this feature as evidence of a cerebral, rather than a hypophyseal origin of the disorder. We accordingly propose to call it the Laurence-Moon-Biedl syndrome, in acknowledgment of its original observers and of its rediscoverer.

Biedl's cases, reported in abstract in 1922,[2] are recorded in detail by Raab.[3]

BIEDL'S CASES. The family history was negative. The mother had 6 normal births and 1 miscarriage. The order of births was as follows:

Girl, aged twenty-two years, first born, *affected.*
Boy; had *polydactylism;* died at age of two years, of pertussis.
Girl; had *polydactylism;* died at age of three weeks.
Boy, normal; died at age of nine months.
Boy, aged sixteen years, *affected.*
Boy, aged fourteen years, normal.

CASE I.—A girl, aged twenty-two years, was a stout child. She has had poor vision in twilight since childhood, and in the last year she has had marked diminution of vision. Obesity has increased since the age of sixteen years. Menstruation began at twenty-one years; the flow was scanty and irregular, appearing

only four times, and has not appeared for one year. She has a wide head, and the head and neck are vertical. The hair on the head is coarse, and there is some hair on the cheeks, chin and upper lip. Axillary hair growth is poor, but there is considerable hair over the pubic region, distributed in masculine fashion. The skin is rough and dry, the face ruddy, and the skin of the chest and extremities is mottled. There is adiposity, especially of the breasts, abdomen (limited by a deep furrow at the mons pubis) and hips. The thighs are massive, but the extremities otherwise are less involved in the adiposity. The hands are short, the joints wide, and the fingers end in knobs. The feet are short and broad and there is genuvalgum of a moderate degree. There is an extra toe on the outer side of the left foot, and syndactylism between the second and third toes of the right foot.

The eyes show a slight divergent strabismus; pupils react poorly to light and convergence. The eye-grounds show retinitis pigmentosa with very little pigment. The vessels in the papillæ are narrow and there is slight sclerosis of the vessels of the chloroid. There is a postcortical cataract; marked limitation of visual fields. Vision: O. D., counts fingers at 15 cm.; O. S., counts fingers at 30 cm.

Teeth are partly defective; thyroid negative; mammæ very obese, nipples without pigment.

Genitalia: Labia majora flat, clitoris small, prepuce hardly apparent, the hymen fleshy. By rectal examination the vagina is found to be short, the uterus small and inclined backward, and the adnexa not palpable.

Roentgen-ray of the skull shows a moderate degree of brachycephaly, with occiput sheer. The sella turcica is small in width and configuration. The dorsum sella is plump and sheer.

Urine examination is negative; blood count is normal; Wassermann reaction negative.

There is mental torpor and a phlegmatic lack of interest. Menses occurred after administration of ovarian substance and then continued without further therapy. Sometimes they were substituted, and always accompanied, by nasal bleeding and headache.

The vision gradually improved under combined pituitary and thyroid therapy, and a gradual loss of weight amounting to 6 kg. occurred.

Case II.—Ernest, aged sixteen years, weighs 54 kg. and measures 141 cm. in height. He has been fat since childhood, and has had defective sight. He is brachycephalic and his occiput is sheer. His hair is dense and coarse; cheeks are red; palpebral fissures narrow; nose short; eyebrows almost absent. He has very little hair on the body. His skin is dry, rough and cold, and over the thorax and extremities is mottled. There is marked adiposity, especially of the mammæ; and the lower extremities are fatter

than his sister's. The legs are column-like, the hands short and the joints broad; the fingers are thick at the base, the tips pointed. There is a sixth finger on both hands. There is slight genuvalgum. The feet are short and broad, and there are six toes on each foot.

Eyes: Pupils react to light and accommodation; there is an *atypical retinitis pigmentosa*. The vessels are broad, and there is abundant pigment; there is postcortical cataract, marked limitation of visual fields; marked diminution of vision. The oral opening is narrow, the teeth good; the thyroid is normal; thorax is short and barrel-shaped; heart and lungs are normal; the mammæ are fatty, the nipples free of pigment. The abdomen is negative.

Genitalia: Scanty hair; there is a cushion-like, overhanging mons veneris and a nipple-like penis; the scrotum is divided into halves by a deep raphé; the testes are the size of beans; the prostate is not palpable.

Roentgen-ray of the skull shows moderate brachycephaly, a sheer occiput, and no evidence of increased intracranial pressure. The sella turcica is of normal width and configuration; the dorsum sellæ is plump and sheer.

Urine and blood examinations are negative; Wassermann reaction is negative.

Mentally the boy is childish and apathetic.

A third case, occurring in another family was likewise reported by Biedl:

A boy, aged thirteen years, showed adiposity (weight 66 kg.) and retinitis pigmentosa. The family history was negative.

Roentgen-ray of the skull showed a thick and plump dorsum sellæ.

Summary of Biedl's Cases. A brother and sister, of a family of 6 living boys and girls of healthy parents, showed atypical retinitis pigmentosa, adiposity, genital dystrophy, polydactylism and mental deficiency. Two others of the family who died in infancy showed polydactylism. (Assuming that these might have developed the full syndrome had they lived, we have the remarkable parallel of 4 healthy and 4 affected children in this group, as in Laurence's and in ours.)

Roentgen-ray of the skulls of the abnormal children showed no definite lesion of the sella turcica, but the dorsum sellæ were plump and sheer. The same was true of a third case occurring in another family. The brother and sister appeared to respond to hormone therapy.

Biedl regards the condition as a distinct syndrome.

Raab's paper, entitled "A Clinical and Roentgenologic Study of Hypophyseal and Cerebral Obesity and Genital Atrophy,"[3] deals with this particular syndrome (of which he states there are

seven certain cases*) only as a part of a larger consideration of dystrophia adiposogenitalis. This he believes is not an unvarying condition, but has as its chief components obesity and genital atrophy or genital hypoplasia. His views, based upon the teaching of Biedl,† may thus be summarized:

In studying the genesis of dystrophia adiposogenitalis it is necessary to take into account the function of the hypophysis. Under normal circumstances the pars intermedia furnishes a secretion which is led off by the posterior lobe and stalk to energize certain metabolic and genitotrophic centers lying at the floor of the midbrain (hypothalamic centers). If by reason of some abnormality, developmental or acquired, this secretion fails (*a*) to reach, or (*b*) to energize these centers, some form of dystrophia adiposogenitalis or of cerebral adiposity will result. There are thus three classes of disorder, according as (*a*) there is disease or defect of the hypophysis (pars intermedia), (*b*) obstruction of the pathway and (*c*) disease or defect of the cerebral centers. For example, tumors within the hypophysis causing injury to the middle and posterior lobes may give rise to the clinical picture from failure of secretion; as may tumors without, from obstruction of the pathway. Internal hydrocephalus may cause the syndrome by pressure on the hypophysis or by obstruction of the pathway, or by direct injury to the basal centers. Lesions or defects of the trophic centers themselves may bring about the symptoms, independently of hypophyseal failure, direct (structural or functional) or indirect (obstruction). Among such cerebral lesions could be: Encephalitic foci, tumors, tuberculosis or syphilis of the base of the brain, traumatism; the defects might be functional failures from acquired disease or disorder, or congenital abnormalities.

The *hereditary* (familial) occurrence of the syndrome may be occasioned by congenital hypoplasia of the hypophysis, by internal hydrocephalus and by anomalies of the skull, such as an abnormally high or massive dorsum sellæ. It will be recalled that in the particular syndrome of which we speak, Biedl stressed the importance of the last factor, that is, the high or massive dorsum sellæ, and Raab reëchoes the emphasis laid upon it as a mechanical element in this congenital form of cerebral obesity. He believes that the skeletal defects, polydactylism, and a high and perpendicular dorsum sellæ are similar anomalies, and that the sellar obstruction stands in direct causal relationship with the adiposity and genital dystrophy. Thus the thicker and more perpendicular the dorsum, and the more extended its contact with the third ventricle, the more

* He does not know of de Schweinitz's cases, of Engelbach's cases, of Laurence and Moon's cases, or of our cases. This brings the record, so far as known to us, up to 20 in all.

† No attempt has been made to preserve in this summary either the author's language or his method of statement.

likely is the syndrome to develop. He believes that pressure occurs at the edge of the dorsum, thus shutting off from the basal centers the energizing secretion of the middle lobe of the hypophysis.

G. E. de Schweinitz, in his Bowman Lecture,[4] speaks briefly of the association of pigmentary degeneration of the retina with pituitary diseases and polydactylism. After citing a case of Bardet's published in a thesis of 1920 (and which is abstracted and included by Raab in cases from literature) he mentions 3 cases of this character that he himself, has seen. One responded well to organotherapy—vision, general condition and mentality showed distinct improvement; in another the effect seemed favorable, but not so pronounced. He suggests that subjects of pigmentary degeneration of the retina who are benefited by the administration of pituitary and thyroid extracts may owe their improvement to the corrective influence of these preparations upon an associated pituitary-body disorder.

Discussion. That the retinal phenomena of the syndrome described by Laurence and subsequent writers and which the cases here reported well illustrate, represent merely one phase of a general developmental failure, seems self-evident, and we need not stress the point further. Retinitis pigmentosa—to use the common term—has a very definite hereditary transmission, is often accompanied by nystagmus, strabismus, deafness, hare-lip, supernumerary toes and fingers and other anomalies; but its particular association with this form of dystrophia adiposogenitalis stands out as a distinct syndrome.*

For the sake of discussion let us accept Biedl's thesis in regard to the cause of cerebral obesity. He contends, it will be recalled, that the secretion furnished by the pars intermedia of the pituitary gland is led off through the posterior lobe and stalk to energize the centers regulating metabolism and genital growth, which are situated at the floor of the midbrain. If (*a*) this secretion fails to reach the centers, or (*b*) if the centers themselves are defective or diseased, and fail to react normally to the secretion, dystrophia adiposogenitalis will result.

We are then left with several possibilities as to the cause and pathological mechanism of this particular syndrome, which is unquestionably of congenital origin. Among such possibilities are congenital hypoplasia of the hypophysis, a high dorsum sellæ obstructing the pathway and congenital defects of the midbrain.

* Thus Stör (Klin. Monatsbl. Augenh., 1865, p. 23; cited Brit. Oph. Rev., 1866, **2**, 203), reporting on a patient with hemeralopia, six digits to each extremity, and mental retardation, does not mention adiposity or defect of the genitals. Höring, (Klin. Monatsbl. f. Augenh., 1865, p. 236; cited Brit. Oph. Rev., 1866, **2**, 408) who found 4 cases of retinitis pigmentosa among 31 defective children in the institution at Stettern, whom he examined with special reference to this affection, mentions an associated feeble-mindedness. According to Nettleship (Trans. Oph. Soc. United Kingdom, 1909, **29**, 37), progressive nerve deafness and idiocy seem capable of acting as mutual equivalents or substitutes in hereditary transmission of the complex associated with retinitis pigmentosa.

Engelbach,* who has seen, but not reported, two cases of this syndrome, has been rather in favor of the pituitary origin of so-called cerebral obesities in general; but perhaps the strongest point against direct pituitary genesis of the syndrome presented in our cases is the normal osseous development, the significance of which Engelbach† himself has specially emphasized.

Our own first tendency in regard to our patients was, indeed, to imagine, in spite of the inconclusive roentgen-ray studies, a congenitally deficient hypophysis. Reflection, while leading us to admit the weight of evidence against this view and in favor of congenital defect of the trophic centers, inclines us, nevertheless, to keep our minds entirely open and await the progress of research. The hypothesis advanced by Biedl and elaborated by Raab is more than highly plausible—it is seductive. But as yet there is no proof from necropsy that in cases like those here reported the hypophysis is not involved in the general imperfection of development. Hence, while we wish to go on record as to the distinctiveness of the syndrome as a pathological entity and the strong possibility of its cerebral origin, we are content to leave the question of the exact mechanism to further study.

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BELL'S PALSY; FOUR CASES OF INFECTIOUS ORIGIN.*

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In the year 1823, Charles Bell, an Englishman of keen powers of observation, noticed that in cases of facial paralysis, whenever the patient tried to close the eyelid of the affected side, the eyeball would roll upward and, upon persistent effort, outward as well. Facial palsy, as it was then called, of unknown, or at least proble-

* Personal communication to one of us (S. S-C.).

† In a recent communication Engelbach and McMahon[5] suggested, after a comparative study by roentgen-ray of the development of the bones in normal persons and in those subject to endocrine disorders, that the information thus gained may be of more value in diagnosis than basal metabolism, blood chemistry and other so-called specific and laboratory determinations.

* Read before the Academy of Ophthalmology and Otolaryngology, September 16, 1924.

matic origin, characterized by this sign came to be called "Bell's Palsy." The French observers in particular were struck by this symptom and due to Bell's persistence and apparent originality of perception consistently refer to it as "the sign" or "phenomenon of Charles Bell." From the very beginning cold was thought to be the cause of this paralysis of the brow, cheek, lip, eyelid, and, when involving that portion of the nerve lying within the Fallopian canal, taste and hearing as well. It is interesting in passing to recall the number and variety of diseases in which chilling of the surface of the body has been from antiquity regarded as causative of disease, whether it be pneumonia or chilblains, acute nephritis or coryza, diarrhea or lumbago. The prevalence of the infectious diseases during cold weather seems to those ignorant of disease processes (not all of them laymen, at that) further proof of this belief, wherein they fail to realize that warm weather brings with it the open window and door, the admission of fresh air and sunlight to which no germ is long resistant.

In the year 1889, both Charcot, the neurologist, and Neumann, the otologist, spoke disparagingly of cold as a cause of facial palsy, and both seemed to feel that an inherited susceptibility to nervous disease was responsible for the paralysis. In support of his belief Neumann gave a history of one family in which three members were afflicted with this disorder. Bell was able to produce experimentally all the classical symptoms by severance of the facial nerve, but, as in the beginning of his observations, he concerned himself chiefly with the eye phenomena. He regarded the rolling upward and outward of the eye as "physiologic," due to the exaggerated effort to bring into play the now paralyzed orbicularis palpebrarum.

It is perhaps almost essential to a proper understanding of the different phases of this paralysis that the course of the nerve involved be clearly kept in mind. The most convenient and logical division for this purpose would seem to be into three sets of branches: (1) Those given off within the Fallopian canal; (2) those extracranial and given off before the terminal division; (3) the temperofacial and cervicofacial divisions. This threefold division is not merely an anatomic nicety, but will explain why some cases of Bell's paralysis show ear symptoms like tinnitus and slight deafness, indicating involvement of the chorda tympani and stapedius, while others are complicated by perversion of taste and impaired motility of the tongue, showing implication of the chorda tympani and glossopharyngeal. Again, there may be nothing but uncomplicated facial paralysis, where the inflammation attacks the nerve after its exit from the stylomastoid foramen.

Careful studies of many temporal bones seem to justify the conclusion that the right stylomastoid foramen is generally more constricted than the left and that this difference is found more often in the female. Thus, these two facts are sometimes regarded as

predisposing causes of Bell's palsy, inasmuch as women are certainly more often afflicted than men, and a narrow canal exit would give a pressure paralysis in the presence of an effusion. Again, clinically, this theory seems to be borne out by experience, as right-sided affections are more often seen in this disease. It is my firm conviction that every case of Bell's paralysis will be found to be of toxic origin, if care is exercised in the search for such a cause. It bears, in several respects, a very striking resemblance to herpes zoster, not the least of which is the cause: infection. I have not seen this comparison drawn by any writer though it is so suggestive that someone must have noticed it long before my time. Herpes was long supposed to be due to exposure to cold and to many other fantastic things, but we now know it to be result of infection of the ganglion. If exposure to a draft or cold wind causes facial paralysis, why doesn't it cause a simultaneous facial neuralgia, as the trifacial nerve is much more easily disturbed by such a cause and is much more vulnerable in the face and temple, by reason of the superficial nature of its distribution? Yet, it does not do so. With a heavy protective coat of bone, periosteum, muscle and skin, is it likely, or even possible, that cold would attack that part of the nerve lying within the Fallopian canal? Yet it would have to do so to cause taste and hearing perversions associated with facial palsy, since a neuritis of the nerve external to the stylomastoid foramen would not give any symptoms other than the paralysis. On the other hand, infection through the blood stream readily reaches any nerve anywhere, and the close confinement in a small, unyielding bony canal to which the facial nerve is subjected, renders a paralysis certain with the slightest effusion into the nerve sheath, such as is caused inevitably by an infection of that nerve. It is interesting to see that some of the older writers have shown sufficient courage and independence to consider "rheumatism" as a cause, and quite suggestive when we realize that cold was thought for many years as a cause, in turn, of this rheumatism. Thus, we gradually arrive at the real cause: infection, which is, of course, the cause of rheumatism. Thus, these gentlemen were not far away from discovering the real cause of facial palsy, though they were in blissful ignorance of their proximity. Of course, syphilis, tuberculosis, pressure by growths, parotitis, encephalitis and hysteria may severally cause a paralysis of the facial nerve, as well as the familiar otitis media in its various forms, but this is not the Bell's palsy of classical renown. Bell himself and his followers referred to a paralysis of unknown or problematic origin.

Most cases of this trouble show either tongue or ear symptoms, or both, associated with the facial distortion; in other words, the neuritis is intracranial, where, as I have pointed out, cold cannot strike, but where infection can easily do so. On the other hand, exposure to cold where a patient is overheated can readily be the

exciting cause of an acute exacerbation of a chronic trouble in the tonsils, teeth or nasal sinuses, and thus bring on a toxic neuritis of the facial nerve. In fact, I was able to demonstrate a definite causal relationship between each of these foci and a Bell's paralysis in the four cases which form the basis of this paper. Not only is this so in these cases, but I go so far as to say that I have never seen a case where I was not able to find an infectious cause. To me it seems the only reasonable explanation and cold at best merely a contributory factor. I have been particularly struck with the invariable presence of the nervous diathesis in every case that I have seen or have had under my own care, though I cannot make myself accept Charcot's belief that this is actually a cause. However, it is a most interesting phase of the disease and certainly exerts some influence on the prognosis and length of convalescence.

Case Reports. CASE I.—M., a highly nervous young man, much overworked, very conscientious in the discharge of his duties and hard pressed to support his family. Here is the clear-cut background of neurosis upon which Charcot lays with much justification such stress. In the course of my examination I observed that he had bitten his nails down deeply, which is merely another nervous sign. He had a complete paralysis, with all the tongue, facial and ear symptoms, of three days' duration when I first saw him. The onset was sudden, and attributed by him to exposure to a draft when he was overheated. He proved to have an acute empyema of the left antrum and acute exacerbation of a chronic tonsillitis. Irrigation of the antrum and swabbing of the tonsils with silver nitrate resulted in marked amelioration of all the paralytic symptoms in thirty-six hours and complete disappearance of all of them in ten days. The antrum was certainly the source of the infection, as his tonsils were not removed and his paralysis disappeared. However, a tonsillectomy should be done, of course, to prevent possible reinfection, and he was so advised.

CASE II.—In B., the nervous element was not prominent but was certainly present. He was a government clerk whose trouble had been well established for four days before I saw him. The mouth and cheek on the affected side were immobile, but the eyelids merely slow in closing, and the tongue only partially affected, there being some difficulty in keeping food out of the hollow of the cheek. The ear was not involved. He had had another attack five years before and attributed both attacks to exposure to cold wind while driving a car. He had buried tonsils with surface plaques of caseous material and palpable glands at the angle of both jaws. I removed his tonsils under novocaine-adrenalin infiltration and in two days the eye was closed easily and normally and in two weeks there were no signs of any paralysis.

CASE III.—G. This man had had his second attack in six months when I saw him, in consultation, and gave as the cause sitting on the ground when overheated from playing golf. I was naturally skeptical, holding the views of etiology that I did, but especially so as the day referred to was very hot and even the ground seemed warm. At this time the cause seemed to me to be the tonsils. His paralysis was absolute, such as is seen only in severance of the nerve, with epiphora and all the other distressing symptoms. The time-honored treatment of strychnin, hot and cold applications and faradism were all tried, and in two months most of the trouble was gone, though it was three months in all before the condition approached normal. Even then the eyelids looked sluggish. I was suspicious of his teeth, but contented myself with a recommendation of tonsillectomy. I lost sight of the case, not being mine, for a year, at which time he had his tonsils removed not for the relief of the paralysis but merely because he felt that his throat was uncomfortable in winter. Three months later a twitching of the mouth and eyelids, difficulty in closure of the eye and inability to whistle made him and his numerous advisors feel that my theory of infection was wrong as the tonsils had been out three months. However, it in no wise vitiated my theory, as I pointed out an upper bicuspid whose removal showed a large apical abscess and resulted in an apparently permanent cure of the paralytic signs. He still has some teeth that I think unsafe and that may cause a recurrence. While outwardly not nervous in the laymen's view of the word, yet this patient is one of the repressed, nervous types whose highly organized nervous system is subject to an exaggeration of subjective symptoms.

CASE IV.—P. This case was seen by me after a week's duration of the paralysis and was most distressing to witness, as she was a pretty woman, very sensitive because of her disfigurement. She had had neurasthenia six months before. The eye signs were most pronounced, chiefly because she had little play of expression and the lips were not so apparent in their sluggish movement. However, her tongue gave her the most trouble as she often bit it while eating and food accumulated in the cheek. She thought her trouble was due to washing her hair and allowing a draft of air to strike her head while wet. There appeared nothing wrong with the nose or throat unless it was a slight redness of both tonsillar pillars, and the small tonsils themselves were free of exudate, but, noticing a slight swelling over an upper molar I elicited the fact that she had had tooth-ache for ten days. A roentgen-ray picture showing some trouble at the root of that tooth, I urged immediate extraction which was followed in two days by relief of the eye symptoms, and in ten days of the whole paralysis.

Conclusion. To the objection that the disappearance of the facial paralysis and the removal of a focus of infection may be merely

a coincidence, and that cases recover without any surgical intervention, the reply is that this disease is singularly intractable under old methods of treatment and singularly amenable to treatment by removal of infection. Under non-surgical treatment requiring from one to six months for either cure or even lessening of the symptoms, and under surgical measures showing improvement frequently in two days and always in seven, with definite cure in twelve to eighteen days, depending upon the duration of the disease before removal of a focus of infection was attempted.

It is here pertinent to state of those conditions in the eye-grounds showing exudate and effects of infection, 60 per cent are due to apical tooth abscesses, 25 per cent to diseased tonsils, about 10 per cent to nasal sinus disease, and the remaining 5 per cent to infection elsewhere in the body, divided among foci in the gall-bladder, genito-urinary tract and the intestinal tract.

So far as clinical evidence can be conclusive, two facts stand out clearly in these cases and in all I ever have seen: (1) The definite connection, or at least presence of infection in cases of Bell's paralysis; (2) the existence of the nervous diathesis. I believe that every case will show some focus of infection, whether it be in teeth, tonsils, nasal accessory sinus or some other place and that such infection is the true cause of every case of what we have recognized since the time of Charles Bell as "Bell's Palsy."

AUTOMATIC SYNCHRONIZATION OF ROENTGEN-RAY EXPOSURES.*

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and

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Theoretical Considerations. Three organ systems, the digestive, circulatory and respiratory, increase the difficulties of securing satisfactory roentgen-ray records because of their physiological movements. Gastrointestinal peristalsis is subject to varied rhythm and intervals, but the movements are slow enough to be followed by the eye and the desired phase recorded by moderately rapid exposure. The two remaining systems constitute interdependent but dissimilar problems. Their interdependence is due to enclosure of lungs, heart and great vessels in one cavity and the

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consequent influence of the activity and condition of each one on all the others. Their dissimilarity is due to their disparity in rhythm and in density, the heart and aorta requiring records with well-defined outlines, the lungs with contrast and detail. The respiratory rhythm is relatively slow, and arrest can be secured, usually in moderate inspiration, for the time of exposure, except in the very young and in cases of severe dyspnea. But the degree of chest expansion varies the tension, and therefore the compressibility and rebound, not only of the lungs, but also of the majority, at least, of the intrathoracic vessels. With the descent of the diaphragm and attached pericardium, the arch of the aorta and the lung root descend, and the thrust of the systolic discharge on the tracheobronchial bifurcation, and especially the left hilum, is increased. Thus, insofar as inspiration increases the tension of vessels about the lung root and throughout the lung substance, it is unfavorable to stillness and to satisfactory roentgen-ray records.

Roentgen-ray films of excised lungs show the radiating trunks in beautiful detail; yet densities of pathological origin are readily distinguished, since the fine normal constituents appear as branching lines and not as a confused blur of uneven mottling, such as commonly results from attempts to secure fine detail in the living. While the intensity of the roentgen rays necessary to penetrate chest walls must always tend to wipe out lung detail in the living, this is somewhat paralleled by the effect of edema almost constantly present in the excised lung.

The most difficult problem has been to catch the lung at rest. In a study of childhood tuberculosis, being carried on in the Henry Phipps Institute, it has been desired to secure records showing the presence and number of primary or focal tuberculous lesions in the lung substance and at the hilum. Most striking evidence of the extent of movement both of the hilum and the lung substance is obtained in these cases from stereoscopic films made in the usual fashion, that is, without synchronism with diastole. Examining a series of such films, one finds commonly in one of the pair the shadow of a calcified lesion, it may be 0.5 to 1 cm. in diameter, sharply outlined, lying 2 to 4 cm. or more lateral to the cardiac or aortic outline; in the other film of the stereoscopic pair, this lesion may be more or less blurred or even quite indiscernible. In the latter case the trunk shadows of the surrounding lung-field are found to share the characters of the outline of the calcified lesion; and usually it may be seen that the cardiac or aortic outline is blurred as well.

Such a finding is frequent even with exposures of 0.05 second, (timing checked against the perforated lead top). Rapid exposure reveals pulmonary densities that are not demonstrable by slower exposures. But it does not appear that rapid exposure alone, with present equipment, will meet the needs. The pulse wave in the large vessels travels some 3.4 to 4 meters per second, and is more

rapid with branching and decreasing caliber;[1] while it appears that the rate of propagation of the pressure in the large vessels may change from 3.2 to 17.6 meters per second. (See Fig. 2 reproduced from Fig. 23, *The Circulation in Health and Disease* (Wiggers).

These enormous changes in pressure, and in the relation of pressure in different vessels, occur in 0.12 second in this record. Subsequently there is a fall of pressure in all vessels; but it is much more rapid in the pulmonary artery than in the aorta, (compare Figs. 1 and 2 (Figs. 22 and 23 of Wiggers' *The Circulation in Health and Disease*). Further disturbances of lung detail may be caused by the vibrations of the blood column following systolic ejection, (see *c'–c*, Fig. 1), the reflection of the pulse wave at branches, and the effect of varying pressures in the curved elastic arteries—an influence insufficiently weighed in the physiology and pathology, especially of tuberculosis, of so mobile, compressible and elastic an organ as the lung. It is possible that the early diastolic rush of blood from the large venous trunks to the auricle also causes vibration of the adjacent lung in individuals with slowly beating hearts. Moreover, ventricular systole endures for 0.33 second, at pulse rates of 60, to 0.23 second at 120;[2] the volume of blood discharged being between 50 and 100 cc;[3] and auricular systole, contributing 18 to 60 per cent of ventricular filling, (proportionately more the faster the heart beat), averages 0.11 second.[4] The minimum of cardiac movement and of rate of change of pressures both absolutely in each vessel and relatively, as between pulmonary and systemic circulation, occurs in late diastole, and this period is therefore the best suited to accurate recording of pulmonary densities, normal and pathological. This period is represented in Fig. 1 as the time between *h* on the right auricle curve and the second *a* on the pulmonary artery curve.

In a study of heart volume changes, Meek and Eyster[5] added synchronism to speed of exposure. Their method was to catch the rhythm of the heart beat heard through a stethoscope and to expose

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FIG. 1.—Pressure changes in the pulmonary artery (upper) and the right auricle (lower). *Upper record: a*, auricular wave; *b*, preliminary vibrations; *c'–c*, sudden systolic ejection throwing the column of blood into vibration; *d*, systolic summit; *e–f*, incisura. *Lower record: a–c*, auricular systole; *c–d–e*, early systolic vibration; *f*, small notch at end of systole; *g*, early diastolic fall, opening of tricuspids; *h*, mid-diastolic wave, occasionally present.

FIG. 2.—Synchronous pressure curves from aorta near semilunar valves (lower) and innominate artery (upper), showing changes in contour of pressure curve in aorta and its immediate branches and variable rate of propagation at different pressure levels. *A–C*, auricular systole; *C–D*, preliminary vibration during isometric contraction; *D–E–F*, primary oscillation; *F–G*, systolic maximum ejection phase; *G–H*, reduced ejection; *I*, incisura; *K*, after vibrations becoming larger in innominate. Velocity of transmission at *D–D*, 3.2 meters per second; at *H–H*, 17.6 meters per second.

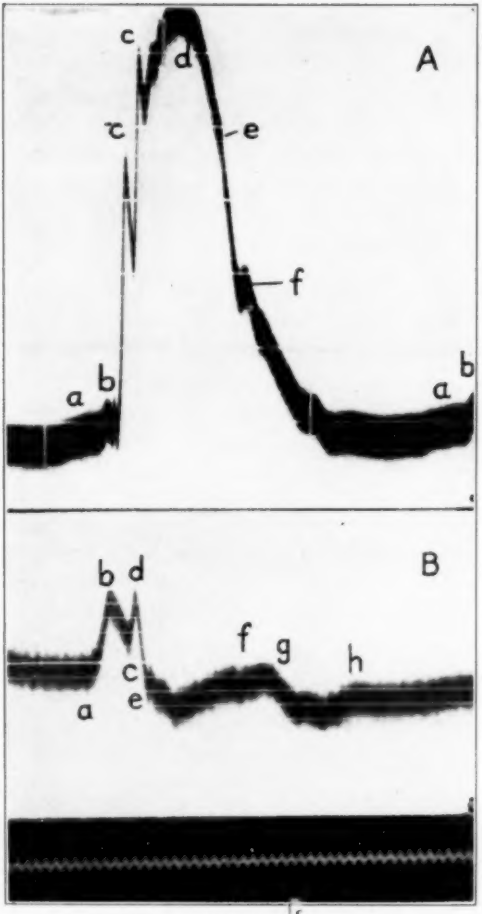

Fig. 1

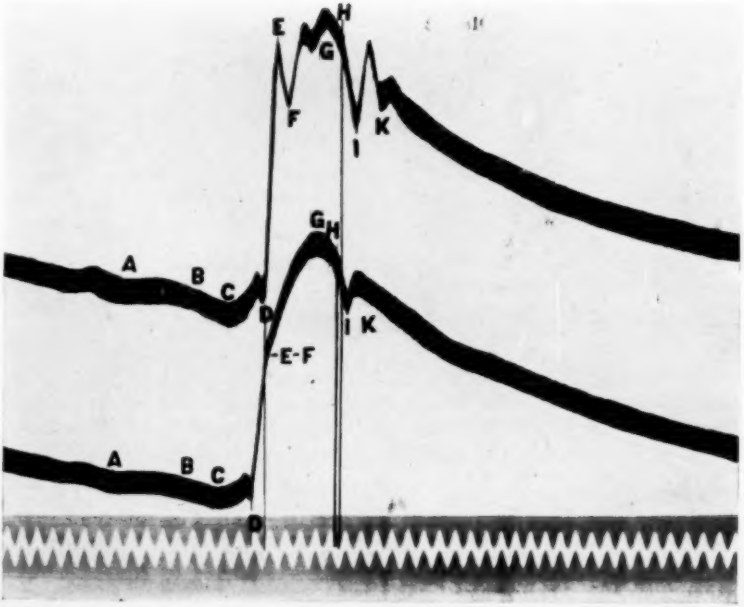

Fig. 2

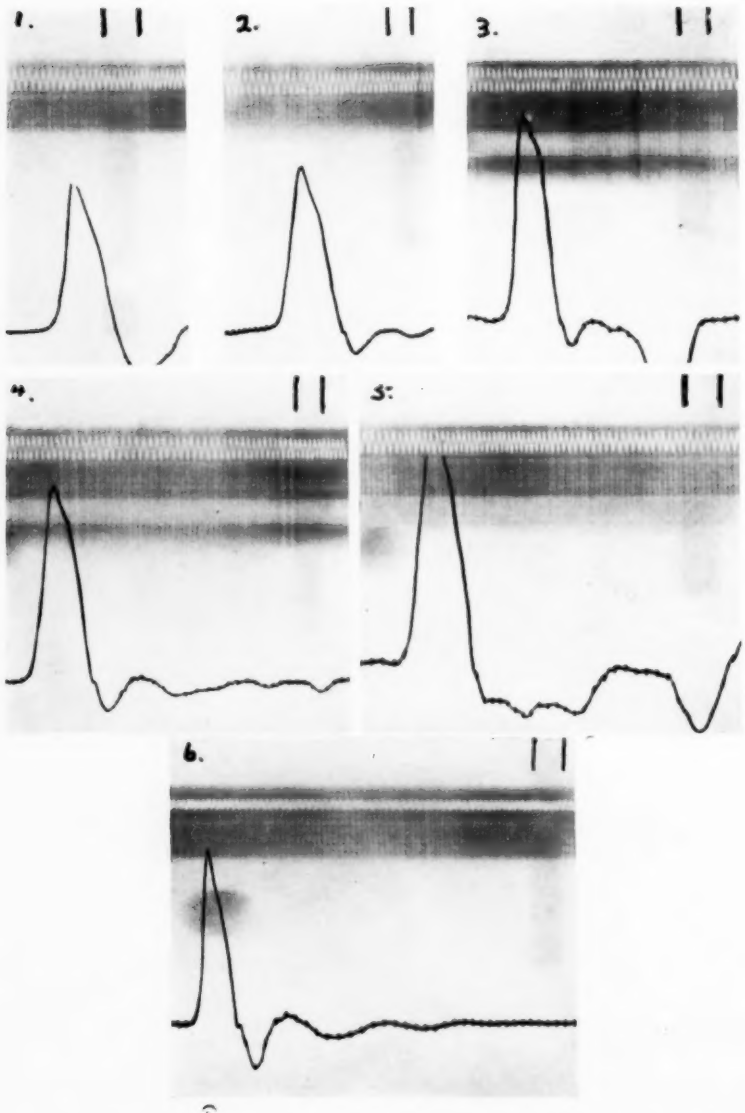

FIG. 4.—Various selected lags between the activating pulsation and roentgen-ray exposure. (1) Lag = 0.084 second; (2) Lag = 0.183 second; (3) Lag = 0.310 second; (4) Lag = 0.435 second; (5) Lag = 0.488 second; (6) Lag = 0.560 second.

at the desired phase by closing the roentgen-ray switch by hand. The period of the cycle exposed was checked by the electrocardiograph. Eyster and Meek (personal communication) also employed excitation of the roentgen ray primary by the heart sounds, using a microphone and relay, but found the apparatus unstable.

For some time hand synchronization of exposure with the period immediately preceding the pulse wave felt at the elbow has been used in the present study of tuberculosis in children. This method is fairly satisfactory with pulse rates below 90, if regular in rhythm. But children, even at fifteen years of age, are readily excited and the cardiac rate becomes rapid. Many of our cases had pulse rates over 100. And irregularity is the rule when the breath is held. When the cardiac cycle is 0.66 second or less the figures of Weitz,[6] Bazett,[7] and others indicate a period of intrathoracic rest of some hundredths of a second. To catch such a period is not possible for the normal muscular reaction, and hand synchronization is ruled out. From these considerations, and because we have long felt that the roentgen-ray record was not as fully complementary to our physical examinations as it was capable of being, we sought means to secure exposures at any predetermined phase of the cardiac cycle. From such records could be obtained true stereoscopic pairs. To meet these requirements one of us (Weyl) has devised a circuit and set up an apparatus by which the roentgen-ray switch can be excited by the pulse wave or the apical thrust. And we have modified a roentgen-ray exposure timer to serve as lag timer, to close the roentgen ray primary at selected intervals after the pulse wave or apex thrust has compressed the air in the receiving tambour.

The Mechanism. The device to be described was designed to expose a roentgen-ray film at any desired phase of the cardiac cycle. It was essential that the device have the following characteristics:

1. Stability;
2. Certainty of operation;
3. Ease of operation.

By stability is meant that the apparatus must respond always to the chosen (cardiac) impulse and never to any extraneous impulse, such as slight involuntary motions of the patient or operator, or to noises in the laboratory.

Certainty of operation demanded not only that the apparatus should always work but that it should always expose the roentgen-ray plate at the exact predetermined time with reference to the cardiac cycle.

Ease of application to the individual case was desirable because the apparatus was required both to ascertain a normal range of intrathoracic cardiovascular movement and, generally, as a routine aid in the study of cardiac and pulmonary disease insofar as the roentgen rays are applicable.

Many methods were carefully investigated employing microphones with vacuum tube amplifiers, the electrocardiograph, the capillary electrometer, but were rejected because of failure to fulfill one or more of the requirements stated above.

The apparatus finally developed is very stable; results are readily and exactly reproducible; and the device is easy to apply.

Reference to Fig. 3 will make the principle of operation clear. Details are omitted in this diagram for the sake of clearness. *L* is a powerful light source, (stereopticon type of incandescent lamp). *C* is a pair of condensing lenses. *M* is a very small galvanometer mirror which is fastened to a flat phosphor-bronze galvanometer suspension ribbon, a horizontal section of which is shown at *U*. The torsion of this ribbon keeps the mirror *M* normally in the position shown in the diagram. *F* is an ordinary glass funnel which is connected to the tambour *T* by means of a flexible rubber tube. The tambour *T* is sealed with a diaphragm *D* of extremely thin

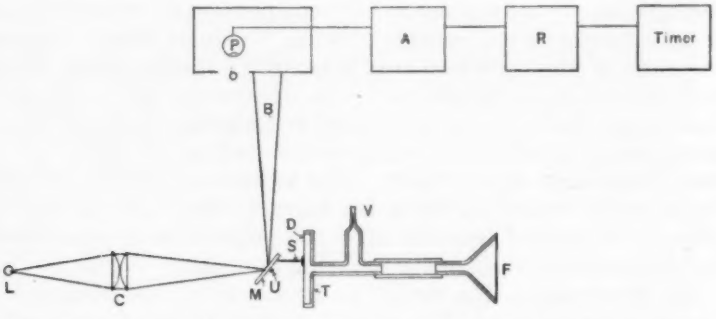

FIG. 3.—Schematic diagrams of apparatus for automatic synchronization.

rubber. By means of a specially constructed lever system, which, for simplicity is represented by *S* in the diagram, any motion of the diaphragm *D* is imparted, greatly amplified, to the mirror *M* which is then rotated about *U* against the restraining torsion of *U*. *P* is a photo-electric cell of the vacuum type, which is contained in a compartment having a light-admitting aperture at *O*. This photo-electric cell is connected electrically to the relay *R* through the vacuum tube amplifier *A*. The purpose of the relay *R* will be made clear later.

If the open end of the funnel be placed against the neck of the patient over the carotid artery, an impulse from this artery will travel through the rubber tube and displace the diaphragm *D*. This will in turn rotate the mirror *M* which deflects the beam of light *B* on to the photo-electric cell, causing a momentary current of extremely small magnitude to flow through the cell. This current which is amplified by means of the single vacuum tube amplifier

closes the relay *R*. This relay *R* closes 0.043 second after the pulse at *F*. This interval can be materially shortened by a somewhat more complicated apparatus. If no greater lag between the carotid pulse (or the apex thrust) and the exposure of the roentgen-ray film is desired, the relay *R* can actuate the roentgen-ray transformer primary directly. If, however, a greater time is desired, it is necessary to introduce a lag-timing device. For this purpose a standard roentgen-ray exposure timer was converted into a lag timer. Instead of having the timer determine the duration between beginning and end of exposure, it was adjusted to determine the duration between the closing of the relay *R* and the beginning of exposure. The length of exposure was controlled by a circuit-breaker.

Referring again to Fig. 3, *V* is an adjustable capillary vent for equalization of the pressure in the tambour, thereby assuring the return of the diaphragm *D* to the normal position after each pulse. The entire apparatus with exception of the funnel and attached rubber tube was enclosed in a light-tight cabinet so that no stray light should affect the photo-electric cell. The electrical connections and the mechanical details of adjustment have been omitted for the sake of clarity and brevity. A full description of the apparatus including constructional details will appear in the near future in an electrotechnical journal.

The Method of Use. There are subjoined (Fig. 4) photographic records of various lags or intervals between the carotid pulsation and the closing of the roentgen-ray primary. From the receiving tambour a rubber tube led to a *Y* tube, one arm connected to a Frank capsule carrying a mirror and set up before the camera: the other arm of the *Y* led to the tambour activating the photo-electric cell. The roentgen-ray exposure is shown as a faint band stretching across the paper, best seen on the white margins; the upper extremity delimited for clearness by ink. The carotid pulse tracing is represented by a dotted line, since an alternating current arc was used for the source of light. The tuning fork has a period of 100. The dark spot on 5 and 6 is due to roentgen ray penetrating the numbering aperture of the camera.

The work of Eyster and Meek has pointed out the value of synchronized roentgen-ray films to establish the volume changes of the normal heart. Only synchronized exposures give comparable records of heart outline to incorporate in clinical records. We are using this method also for study of the aortic arch and for lateral records of the tracheobronchial glands. Its usefulness for the lower half of the lung-field (for example, bronchiectasis) is greater than for the upper, partly because of cardiac movement and partly since the volume, and therefore the elasticity, is greater, and the vessels are longer.

Deductions drawn from the appearance of the hilum shadow are questionable unless the exposure is diastolic. Much of the "broad-

ening and thickening of the hilum" is artefact due to cardiac and aortic pulsation. And it appears probable that much of the "peritruncal thickening of ascending trunks" is also due to vibration. No instance occurs in a study of 318 excised lungs, and it has not appeared in satisfactorily synchronized exposures of the living.

It is just possible that synchronization may be helpful in gall bladder work since the aortic pulsation will be somewhat communicated through the air-containing viscera.

A subsequent article will deal with calibration.

We wish to express our indebtedness to Dean Harold Pender of the Moore School of Electrical Engineering for his interest and advice, and to Prof. H. C. Bazett of the Department of Physiology for suggestions as to timing and recording methods for calibration and for helpful references to the literature.

Summary. Roentgen-ray records of the heart and lungs lack in definition and in comparability, by reason of cardiovascular movement.

A mechanism is described by which exposures may be made at any selected phase of the cardiac cycle.

Systolic and diastolic cardiac outlines are reproducible at will.

Pulmonary records can be made when cardiovascular movement is at the minimum.

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ELECTROCARDIOGRAPHIC STUDIES OF THE EFFECTS OF ETHER UPON THE LIVING CAT'S NORMAL HEART.*

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Our interest was directed to the influence of ether upon the living cat's heart while investigating this organ electrocardio-

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graphically for the effects of ouabain in etherized cats. Cardiac irregularities were encountered, and an attempt was made to determine whether these derangements were caused by ouabain alone, by ether alone, or by a summated result of both drugs. Obviously, therefore, it was important to establish what the electrocardiograms of a normal cat's heart would be, the animal receiving no drug.

To this end a simple box was devised, into which a cat could be placed. The limbs, though fixed by strings, were readily accessible, the neck was firmly held and the animal kept in one posture by tying down the movable lid of the box at an adjustable angle. In this box the animal would remain quiet and undisturbed while the electrocardiograms were taken. The limbs of the animal were carefully shaved and wrapped with 3-inch wide flannel bandages, soaked in hot hypertonic salt solution. The bandages were led off from the wrapped-up shaved areas of the limbs to basins containing hot hypertonic salt solution and saline-filled porous jars; the bandages were partly immersed in the jars and the basins. Adequate protection was secured by rubber sheeting wrapped about the flannel-bandaged limbs, thus keeping the bandages warm, preventing dripping and short-circuiting. Before proceeding with the actual experiments the three leads were taken in the usual fashion. In all instances they were standardized, so that 1 cm. deflection equalled 1 millivolt of current. The galvanometer used was the large-size Williams-Hindle apparatus, the string's resistance being 6400 ohms. In a few experiments the Cambridge outfit was employed in a similar fashion. The standardization was maintained at 1 cm. for each millivolt of current, except in rare instance where time was pressing because of the precarious condition of the animal. Whenever normal standardization was not possible this condition was indicated at the beginning of each record. After taking the normal records the protocols of each experiment were carried out. Lead II was the usual derivation recorded unless otherwise stated.

In this manner 5 cats (Group A) were observed: Cats 105 (Ekg. 19), 113 (Ekg. 24), 116 (Ekg. 25), 117 (Ekg. 26) and 147 (Ekg. 50). As far as could be ascertained, these animals had never been employed previously in any experiments. Three additional cats, 130 (Ekg. 37), 131 (Ekg. 38), 145 (Ekg. 48/02), are placed in Group B. These animals had received ouabain in water or in oil, intramuscularly, but were not studied for any ether effects until several days (two days for Cats 130 and 131 and six days for Cat 145) had elapsed after the administration of the digitalis bodies, and until, clinically and electrocardiographically, no drug effects could be detected. An analysis of these records is given in Table I, and permits the following conclusions regarding the usual characteristics of the normal electrocardiograms of the cat:

TABLE I.—GROUPS A AND B.

Ekg. No.	Cat No.	Date, 1923.	Ld.	*P*.	*R*.	*T*.	Rt.	Electrocardiographic changes.	Remarks.
19 ..	105	Feb. 9	1	−	−	+	250	Regular rhythm	Female; tightened on back to wooden board.
			2	+	+	−	230		
			3	+	+	−			
24	113	Feb. 14	1	0	+	−	270	Regular rhythm; no iso-electric period	Female; placed on abdomen in box.
			2	+	+	−	270		
			3	+	+	−	270		
25 ..	116	April 9	1	+	+	+	..	Low voltage	Male; placed upon abdomen in box.
			2	+	+	0			
			3	+	+	0			
26 ..	117	April 9	1	±	+	0	210	In Lead I doubtful ventric. extrasystole; no special significance; probably due to muscular movements	Same cat had been used for Ekgs. 26 and 38; after 26 it received ouabain; it was used again without ouabain for Ekg. 38; female; placed upon abdomen in box.
			2	+	+	−	200		
			3	+	+	−	200		
38	131	April 18	1	0	±	0	280	Regular rhythm	
			2	+	+	−	280		
			3	+	+	−	270		
50	147	May 10	1	0	−	+	200	Regular rhythm	Female; placed on abdomen in box.
			2	+	+	+	200		
			3	+	+	+	200		
37 ..	130	April 18	1	0	−	+	270	....	Female; placed on abdomen in box.
			2	+	+	±	230		
			3	+	+	−	240		
48 (1)	145	May 3	1	+	−	+	170	....	Male; placed on abdomen in box.
			2	+	+	+	170		
			3	+	+	+	170		
48 (2)	145	May 3	..	..	..	..	..	Was taken 5 min. after 48 (1), with same result	

Ld., lead; +, upward; −, downward large; 0, zero.

(Group A consists of 5 animals never used before experimentally. Group B consists of 3 animals used for ouabain experiments, but rested a sufficiently long time for effects of the drug to disappear. In none of these 8 cats was a drug given during the taking of the electrocardiograms.)

1. In Lead I there is no constant form or direction of the *P* wave or of the main ventricular deflection. The *T* wave could rarely be identified. The electrocardiographical picture varied in almost every animal. This lead, therefore, cannot be used in evaluating a standard electrocardiogram for the normal cat's heart.

2. In Leads II and III the *P* and *R* waves were upright. The *T* wave was downwardly directed or negative in 62.5 per cent of the cats examined.

3. The heart-rate ranged, as a rule, from 200 to 270 (mostly 200). It was 170 in Cat 145 (Ekg. 48). In a number of the cats

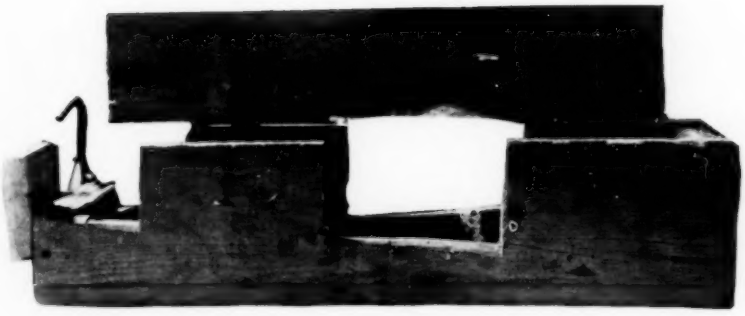

FIG. 1

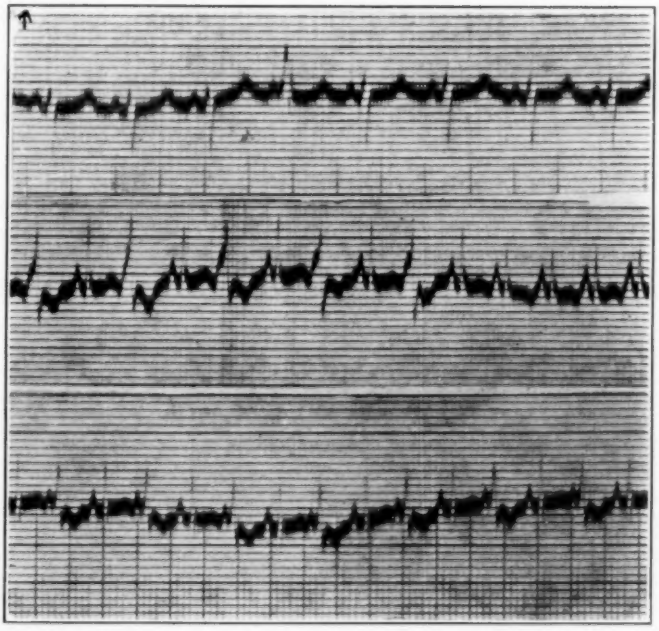

FIG. 2.—Ventricular extrasystoles. Ekg. No. 50 of Cat 147. The first record shows a single extrasystole. The second record shows in its first part extrasystoles alternating with normal beats; the later portion shows again an occasional extrasystole. In the third record a return of the alternating extrasystole takes place upon renarcosis of the animal. Chart II presents the further details of this experiment.

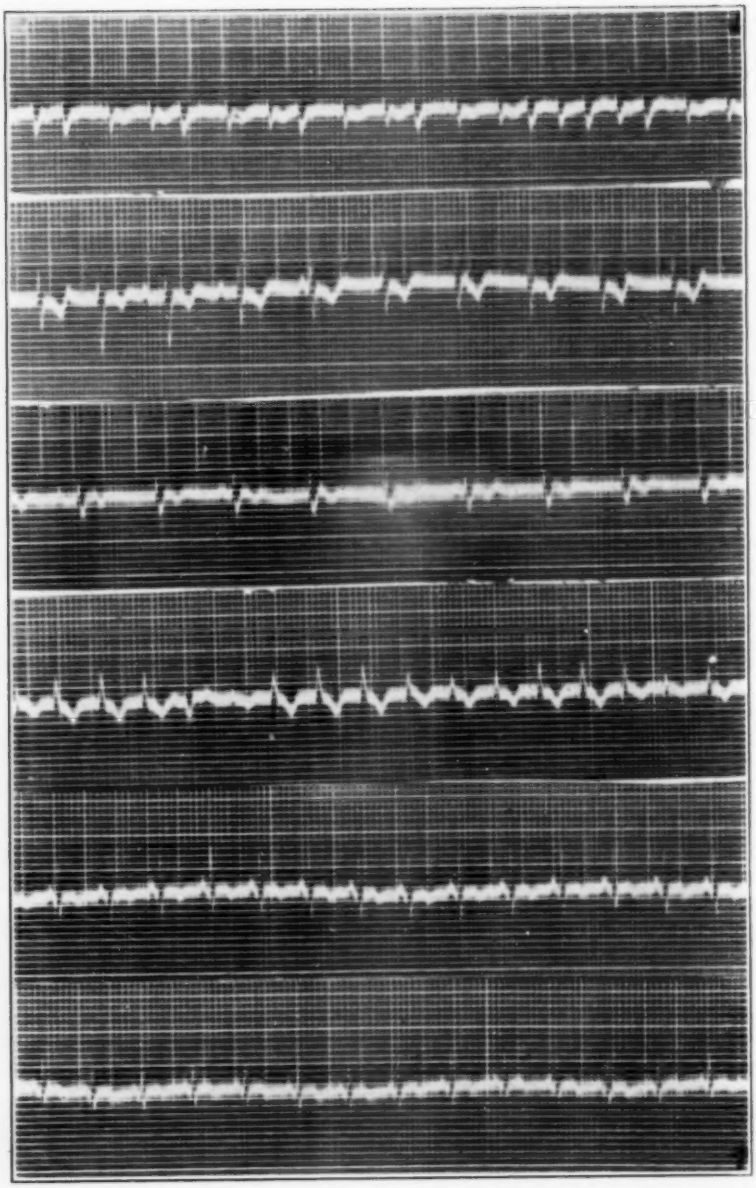

FIG. 3.—Ekg. No. 14 of Cat 100. The first record shows the irregularly acting heart with no evidences of auricular activity (auricular fibrillation). In the second record a high degree of conduction defect is seen in part of which the auricular complexes are submerged; slight evidences, however, can be made out in the deeply inverted *T* waves. There are also regularly recurring changes in the form of the *R–S* deflections. In the third record a 2–1 heart-block is evident, while in the fourth record a rapid nodal rhythm has developed with a curious alternation in the directions of the *T* and *R* waves. Finally, the normal mechanism reasserted itself, as seen in the last two records, upon recovery from anesthesia. Chart III is the protocol for this experiment.

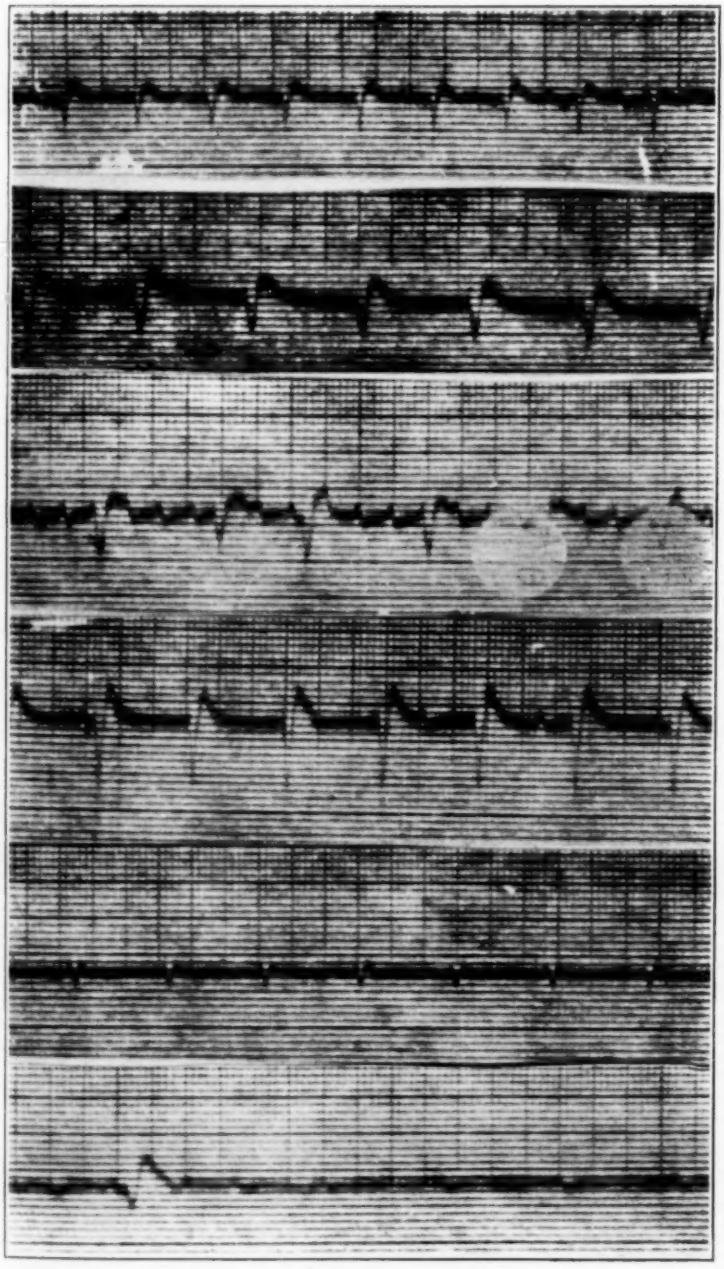

FIG. 4.—(See description on page 520.)

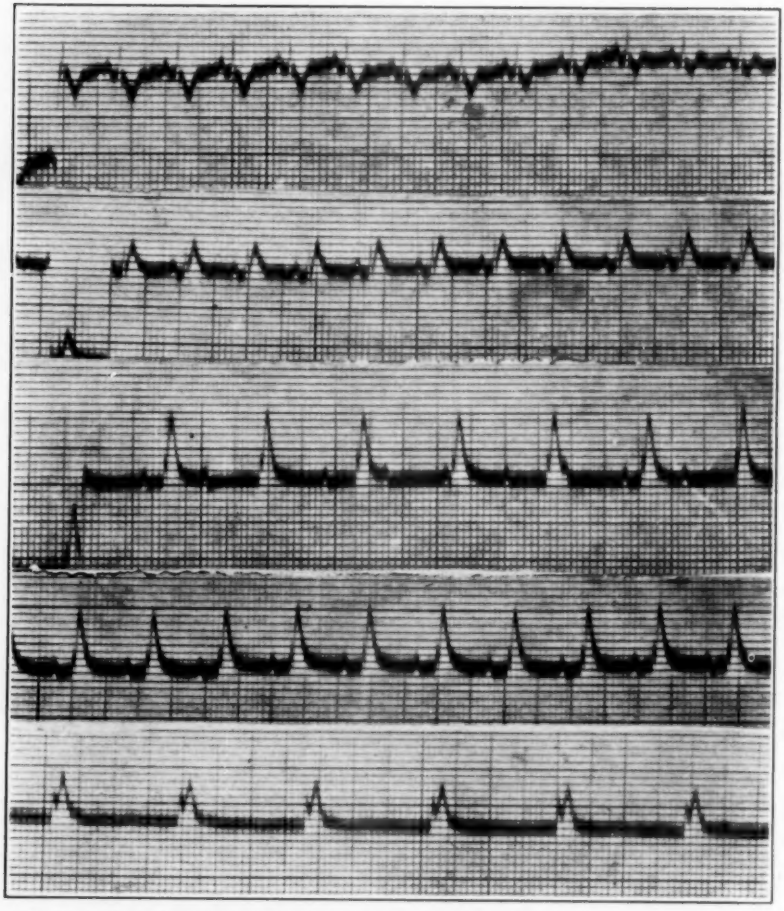

FIG. 5.—Ekg. No. 49 of Cat 146. This series of records shows a gradual change in the form of the *R-T* complex, the onset of a heart-block with a final idioventricular beat, and a complete absence of auricular activity. Record 1 exhibits the *T* wave gradually assuming an upright form from a deeply negative one. Record 2 is a continuation of 1, the *T* wave has now become part of the *R* and continues to rise until it is larger than *R*. Record 3, the *T* wave now overshadows *R* which appears as a notch on the up-stroke of the *T*. The *P-R* interval has progressively increased and in the fourth record a gradual onset of heart-block is seen with a slowing of the entire heart cycle. Record 5 exhibits an abnormally wide and notched ventricular complex; there are no evidences of auricular activity. See Chart V for protocols.

spontaneous variations in the rate of the heart-beat were noted during the periods of examinations.

4. The rhythm was regular in all these cats except in Cat 117 (Ekg. 26). This animal also had a wide *R* and a curious form in its *R–T* complexes, that is, the *T* wave joined the *R* wave before the base line was reached.

Discussion. We may, perhaps, assume when an apparently healthy normal cat is held securely in a simply contrived box, such as the one figured in the text, and when the animal has received no drug whatsoever, or even when a drug like ouabain is given, but sufficient time has been allowed for the drug to become eliminated, or for its effect to disappear, such an animal will exhibit in its electrocardiograms, when taken by the usual three leads, a regular cardiac rhythm, a heart-rate of approximately 200 beats per minute, with frequent inversion of the *T* wave in Leads II and III, and changes always in Lead I, of so diversified a character, as to permit of no constant interpretation. We have observed no "great frequency of spontaneous rhythm,* no spontaneous bigeminy." On the other hand, spontaneous changes in the rate are very frequent.

To properly determine any electrocardiographic effects upon an experimental animal such as the cat, an unanesthetized animal is preferable. Even small amounts of an anesthesia may add electrocardiographic changes that cannot be separated from those caused by a drug or any procedure under investigation. This point we shall try to demonstrate later in the text.

In a consideration of the probable influence of ether upon the living cat's normal heart, *in situ*, a prime difficulty lay in procuring an accurate means of giving ether in exact doses as an inhalant

* S. A. Levine (Jour. Exper. Med., 1919, **29**, 485) writes of the frequency of spontaneous nodal rhythm in the normal cat's heart. A perusal of the text of his carefully conducted work indicates that all cats used by him received ether narcosis in order to permit the undisturbed taking of electrocardiograms. In reply to an inquiry from us as to whether electrocardiograms were procured in normal cats uninfluenced by an experimental procedure whatsoever, Dr. Levin was good enough to write as follows: "Concerning the occurrence of nodal rhythm in cats, I remember distinctly that occasionally this was found even before any anesthesia was administered. Unfortunately, in the table I published in the article that you refer to, one could not be certain whether nodal rhythm developed before or during the anesthesia. I feel sure that it was not rare to find this arrhythmia in the first tracing taken before any drug at all was administered. I have since twice seen it occur spontaneously in cats. We had similar experiences studying the electrocardiographic tracings of patients during operation (Arch. Int. Med., 1922, **30**. 57). I feel that it is a fairly common spontaneous arrhythmia both in normal people and in animals. Just yesterday I took a tracing of a normal dog as a control and happened to find nodal beats. This dog had received no anesthetic of any kind, either local or general." We wish to comment in this connection that in the study of a small group of cats unanesthetized and untouched by any drug, little or no change could be discerned in the electrocardiographic pictures of their hearts. In view of our experiments that increased amounts of ether can produce distinct and striking cardiac disturbances we hesitate to exclude the possibility that so-called spontaneous heart derangements may not be due to narcosis.

narcotic. It is well known that cats take ether easily, that anesthesia is obtained promptly, but that evenness in anesthesia calls for skill and constant vigilance. Not infrequently do cats suddenly die from seemingly small additional amounts of ether. We studied theoretically several means for administering ether in a quantitative way, but they seemed to be cumbersome and unsatisfactory. Eventually, therefore, we were compelled to resort to the crude drop-cone method as the only practical procedure. The respiratory excursions, the color of the mucous membranes and of the tongue, the amount of salivation, the status of the reflexes, especially the corneal and pharyngeal, these were our guides in estimating the depth of the anesthesia. For practical purposes they served fairly well.

The animals were enclosed in the box previously described or were attached to a board, allowed to grow quiet and relaxed, then anesthetized with ether. Ether was given in changing degrees of concentration and over varying intervals of time. In some experiments we tried to give continuously a so-called "light anesthesia," or "moderate anesthesia," or "deep anesthesia." These terms though loosely employed, signify in a measure a quantitative difference in the type of anesthesia obtained. Again, some cats were started with light anesthesia and the narcotic increased in crescendo fashion until profound anesthesia was obtained; sometimes death resulted. The reverse procedure was also carried out, that is, an initial deep anesthesia, gradually diminishing the amount of anesthesia until the cat recovered completely. Finally, some animals received alternating brief light anesthesia followed by quickly produced deep anesthesia, or *vice versa*.

Cats 99 (Ekg. 13), 100 (Ekg. 14) and 101 (Ekg. 15) were attached to a wooden board. Cats 145 (Ekg. 48), 146 (Ekg. 49) and 147 (Ekg. 50) were placed on their abdomen in the box. Cats 99, 146 and 147 were never used before; Cats 100, 101 and 145 were ouabainized in previous experiments. Charts I and II illustrate the effects

FIG. 4.—Ekg. No. 15 of Cat 101. These records show very remarkable and pronounced electrocardiogram changes induced by deep and fatal narcosis. The records were taken almost continuously. Record 1, only an occasional auricular complex is visible, the ventricles beating regularly at 105 beats per minute; the *T* wave rises directly from the stem of the *S* wave. Record 2, heart-rate is much slower, the auricles are at a standstill and the ventricular complexes are abnormally widened, and the *T* wave is blunt and directly continuous with the *S* wave. Record 3, a remarkable and abrupt change takes place; the auricular activity has returned but as an auricular flutter; the deflections are diphasic, 300 per minute and regularly recurring; some of these fall upon the *R* and *T* waves, distorting them; the ventricular complexes have not changed from that seen in Record 2, and are beating at 83 per minute. Record 4, the ventricular complexes are now of higher amplitude and still abnormal; there is a complete heart-block. Record 5, only auricular complexes are observed; the ventricles are now at a standstill. Record 6, only irregular, variable, small oscillations are visible, the origin of which it is not possible to determine. See Chart IV for protocols.

of varying amounts of ether anesthesia on the normal living cat's heart. The animals were narcotized fully, but only for a very brief period, and immediately allowed to come out of the anesthetic.

CHART I.—CAT 99. ELECTROCARDIOGRAM 13 (NOT PRINTED IN THIS ARTICLE). DECEMBER 23, 1922.

Record No.	Time, P.M.	Electrocardiographic changes.	Anesthesia.
0-1 . .	3.50	Variations in height of *R* and *S* waves in all three leads, *S* predominating	Cat deeply under ether; at end of record out of anesthesia; eye reflexes active.
1-1 . .	3.55	Variation in depth of *S* is marked, especially in Lead II	Deeply under; no eye reflexes.
1-2 . .	4.03	Increase in rate; respiratory variations in *S* were less marked; *T* wave toward end of record became distinctly negative in Leads II and III	Deeply under.
1-3 . .	4.07	Variation in depth of *S* wave marked; *T* wave again upright; *S* wave increased in size	Respirations regular and eye reflexes present; at end of record moving legs.
1-4 . .	4.10	No change	As above.
1-5 . .	4.13	Respiratory variations in *S* wave	Cat came out of anesthesia; reflexes all present.
1-6 . .	4.16	Slight respiratory variations in *S* wave	Almost out of anesthesia.

Résumé. During the height of general anesthesia there were marked variations in the size of the *S* wave. These were distinctly of a respiratory type. Also changes in the direction of the *T* wave were noted, becoming negative but promptly recovering its upright direction with the cessation of the anesthesia.

The following charts, III, IV, V and VI, are protocols of Cats 100 (Ekg. 14), 145 (Ekg. 48) 146 (Ekg. 49) and 101 (Ekg. 15). The animals responded by cardiac disturbances of serious nature, varying in degree and type directly with the amount and duration of the ether narcotic administered. Some were anesthetized up to death and the progressive changes recorded continuously.

In these experimental records we see that during light anesthesia (analgesia) minor electrocardiographic changes, such as variations in voltage, sinus arrhythmia and changes in the direction of the *T* wave occur. An upright *T* is likely to become isoelectric or even negative, while the reverse is true of an originally negative *T* deflection. Inversion of an upright *T* is considered a very important evidence of digitalis effect. In view of the above experimental findings with etherized cats, for experiments with digitalis bodies employing such narcotized animals, this change in the *T* wave evidently should not be used to evaluate digitalis effects.

CHART II.—CAT 147. ELECTROCARDIOGRAM 50. MAY 10, 1922.

Record No.	Time, P.M.	Electrocardiographic changes.	Anesthesia.
0–1 . .	3.33	Normal Ekg. Lead I deflections are however poor and of very low voltage	At 3.31 light anesthesia for 2 min., then no anesthesia; cat out at 3.33.
0–2 . .	3.35	Same as 0–1	Anesthesia continued and then interrupted for 1 min.; eye reflexes present.
0–3 . .	...	Same as 0–1	Moving limbs.
0–4 . .	...	Sinus variation	As above.
0–5 . .	3.47	Variations in the height of *R* and sinus variations	Almost out of anesthesia.
0–6 . .	3.57	Cat's movements distort the electrocardiograms; *T* wave is now iso-electric	As above.
0–7 . .	4.05	Same as 0–6	Moving about actively.
0–8 . .	4.12	In groups of from two to twelve beats ventricular extrasystoles alternate with a normal beat	Anesthesia deepened; no anesthesia was given from 0–2 to 0–7.
0–9 . .	4.25	Sinus arrhythmia; *T* wave flat single extrasystole in Lead I	As above; 50 min. of light anesthesia (first stage).
1–1 . .	4.36	Normal ekgs.; *T* flat	Considerable salivation and eye reflexes present in 1–1; no reflexes during 1–2 and 1–3.
1–2 . .	4.36	Normal ekgs.; *T* flat	
1–3 . .	4.38	Normal ekgs.; *T* flat	
	4.38 to 4.40	No records taken	Ether for 2 min.
1–4 . .	4.40	Long-continued series of alternating extrasystoles, identically like those in 0–8; later record shows a normal mechanism, very rapid 250, with an inverted *T*; gradually this tachycardia slowed down to 187, and *T* wave became upright	Deeply under; no ocular reflexes.
	4.45	.....	Pupils dilated; cat out of ether.

Résumé. A very remarkable repetition of the ventricular extrasystoles was produced during anesthesia, with changes in the *T* wave during the stage of deepening anesthesia and recovery therefrom.

During slightly deeper anesthesia, ventricular extrasystoles and varying degrees of depression of the conduction system were noted from a simple prolongation of the *P–R* interval to a complete heart-block and even standstill of the ventricles for long periods. Also high-grade toxic effects in the form of the ventricular deflections were repeatedly seen. It is not our purpose at present to attempt a discussion whether these changes are directly the result of the anesthetic or whether they may be in part explained by other factors, such as an increase in the carbon-dioxide concentration in the blood or an anoxemia as experimentally shown by Greene and

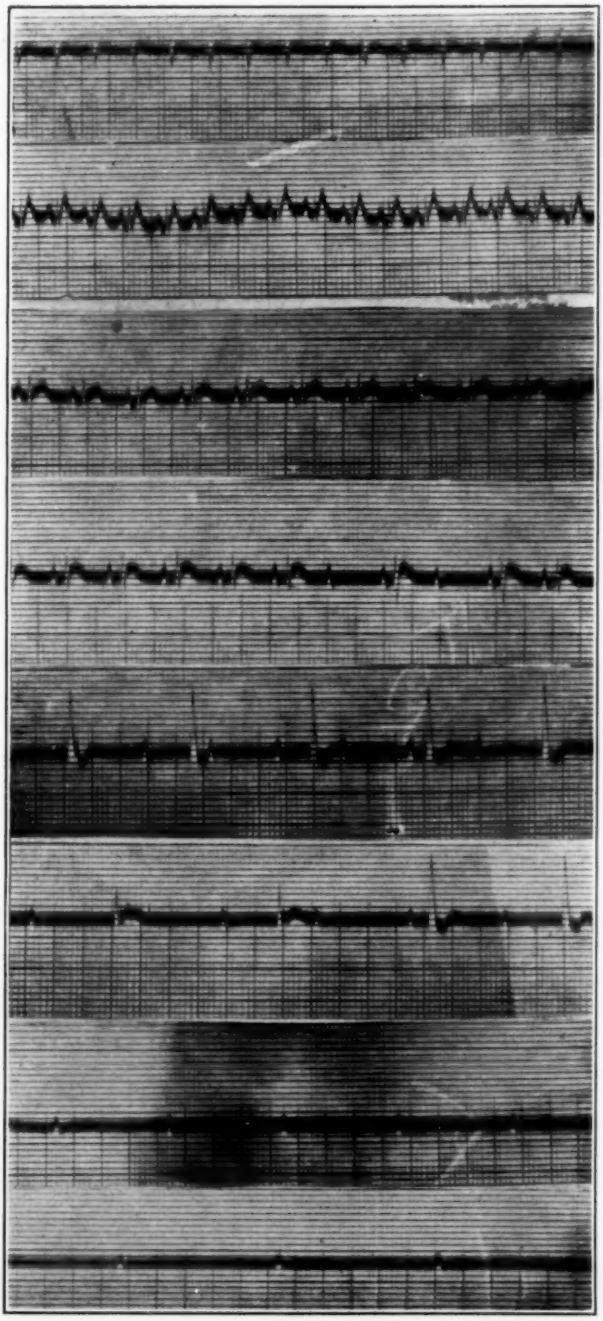

FIG. 6.—Ekg. No. 48 of Cat 145. These records exhibit a gradual slowing of the cardiac cycles with a progressive conduction disturbance until a heart-block is established in Record 4. In Record 5 the block has become complete with a slow auricular rate and an idioventricular beat of abnormal character, resembling that seen in bundle branch block. In the sixth record there is only an occasional idioventricular beat; the majority of the beats are of supraventricular origin, however. Finally, in Records 7 and 8 ventricles cease to beat and only a slow auricular response is seen. Protocol in Chart VI.

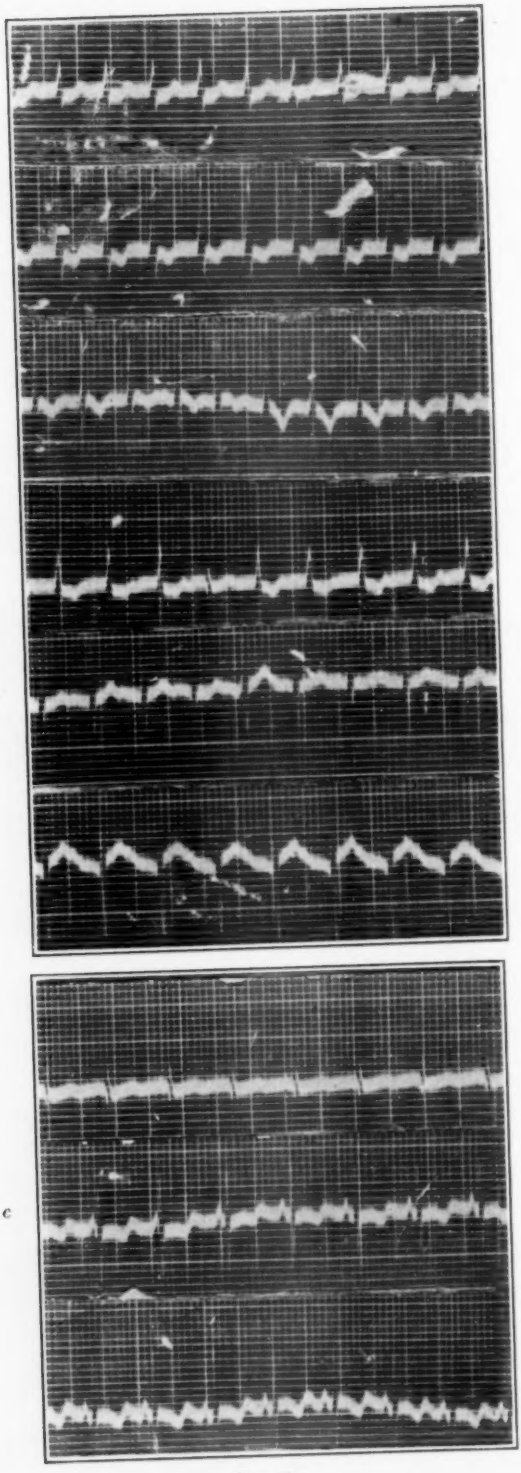

FIG. 7

CHART III.—CAT 100. ELECTROCARDIOGRAM 14 (SEE PRINTS). DECEMBER 23, 1922.

Record No.	Time, P.M.	Remarks.	Anesthesia.
	4.20	No records taken	Anesthesia begun.
2–0 and 2–1 . .	4.31 to 4.33	Auricular fibrillation in Lead I; in Lead II a high-grade defect in the conductive system was seen; in the first 4 beats the *P* wave was apparently submerged, possible evidences being indicated by slight variations in the deeply negative *T* waves; the next 4 beats showed unmistakable conduction disturbance; gradually the *P–R* interval shortened and the *R–S* phase varied in a progressive manner; the next 5 beats repeated the condition of the first series exactly and then a second series was repeated; this alternation of event continued for a considerable time	Anesthesia was deep; respiration stopped during Lead II and were very irregular in Lead III.
2–2 . .	4.35	A slow regular mechanism	Reflexes returned; cat licking its nose; no anesthesia.
2–3 . .	4.45	Partial heart-block 2 to 1	Again was brought deeply under anesthetics; respirations irregular, deep and slow; anesthesia discontinued.
2–4 . .	4.50	Regular normal mechanism returned; slow rate; all deflections increased in amplitude.	Cat out and moving about.

Résumé. This table demonstrates clearly the effects of deep anesthesia, the rapidity of onset of these effects, and the promptness of recovery. During deep anesthesia an auricular fibrillation occurred. In the stage of recovery from this anesthesia a curious series of events followed: First a high-grade depression of the conduction in the bundle of His developed, giving an interesting group of alternating electrocardiographic pictures due to the variations in the degree of this depression of conduction. Then the normal sino-auricular mechanism of the heart-beat returned, and the animal recovered from the anesthesia. When the animal was again deeply anesthetized a partial heart-block ensued, 2 to 1 in character. This was followed by a nodal rhythm previous to the recovery of the normal mechanism for the second time. Marked changes in the direction and the amplitude of the *T* wave were seen during the different degrees of anesthesia.

FIG. 7.—9.52 A.M.: A cat of 1645 gm. received intramuscularly 66 per cent of a minimum lethal cat unit dose of ouabain in oil; a small amount of ether was given to facilitate the handling of the animal; at 11 A.M. there was vomiting; at 5.32 P.M. ether was administered. 5.37 P.M.: Ekg. No. 12 (*a*) was taken while the cat was still slightly under the effects of ether; Leads I, II and III show nodal rhythm (no *P* wave is discernible); in Lead III there is an abrupt change in the direction of the *T* wave, and then gradually recovery to normal condition. 5.39 P.M.: Ekg. No. 12 (*b*) was taken as the cat was recovering from its anesthesia; this tracing demonstrates strikingly the variability in the height of *R*, *S* and *T*; nodal rhythm still persists; *T* is oppositely directed as compared with Ekg. No. 12 (*a*). 5.41 P.M.: Ekg. No. 12 (*c*) was taken while the cat was practically completely recovered from anesthesia; here *P* is distinctly returned; *T* is directed as in the first series; it will be noted that the nodal rhythm disappeared as the animal recovered from its ether anesthesia.

CHART IV.—CAT 101. ELECTROCARDIOGRAM 15 (SEE PRINTS). DECEMBER 30, 1922.

Record No.	Tme, P.M.	Electrocardiographic changes.	Anesthesia.
1–0 . .	4.00 4.15 to 4.20	*T* wave iso-electric in Leads II and III *R* wave low voltage	Anesthesia started. No anesthesia during the taking of records; eye reflexes present; moving legs; additional anesthesia was given toward end of record.
1–1, 1–2 and 1–3	4.25 to 4.32	*R*, low voltage; *T* iso-electric	Same as 1–0; the cat was deeply anesthetized and then allowed to come out.
1–4, 1–5 and 1–6	4.45 to 4.57	Low voltage more marked; slight variations in *P*–*R* interval	No anesthesia; no reflexes; just after Lead III cat opened eyes and moved limbs; anesthesia again given until deeply narcotized; no visible breathing during the taking of 1–6.
1–7 .	5.03	Bradycardia; *P*–*R* increased to 0.2 sec.; *R* abnormal; heart-rate fell to 70; *P* not visible in Part I; *R* deflections became negative, with a large sweeping *T*—a diphasic ventricular deflection; a little later the *R* wave again became upright but no *P* oscillations were recognizable. The next strip showed entire change in mechanism; auricles were well represented, beating at the rate of 300 per minute—"auricular flutter;" the *R* was inverted during this period	Deeply under anesthesia; no breathing; tongue deeply cyanosed.
1–8 . .	5.05	A slow idioventricular rhythm with a diphasic ventricular response (negative *R* and positive *T* waves); occasional auricular wave was seen	Very little breathing; occasional gasps.
2–0 . .	5.09	Occasional *P* visible; ventricles responded as at end of 1–8	No heart sounds audible.
2–1 . .	5.11	Diphasic ventricular responses more pronounced, wider and deeper; very few auricular complexes seen	
2–2 . .	5.21	*R*–*T* very wide, notched and low voltage; *P* less frequent and finally it was represented as a small irregular oscillation seen at a more rapid rate and interrupted by an infrequent diphasic ventricular wave; all deflections ceased	Chest opened; occasional beat observed in the left auricular appendage.

Résumé. During the stage of what may be considered and loosely termed a "surgical anesthesia," minor changes in the electrocardiograms were noted: a slight variation in the *P*–*R* interval and a lowering of the voltage in the *R* wave. During deep and almost overwhelming anesthesia a heart-block developed with later a complete arrest of auricular activity and a slow idioventricular rhythm resulted. A moment after this the auricles went into a state of flutter, beating regularly at the rate of 300 per minute, the ventricles responding irregularly at about 106. This condition lasted only a short time, the auricles continued to beat slowly and infrequently, while the ventricle activity soon disappeared entirely. When all oscillations stopped in the electrocardiograms the chest was laid open and an occasional quiver was observed in the left auricular appendage.

CHART V.—CAT 146. ELECTROCARDIOGRAM 49 (SEE PRINTS). MAY 3, 1923.

Record No.	Time, P.M.	Electrocardiographic changes.	Anesthesia.
	4.45 to 4.46	.....	Light anesthesia begun; no records were taken.
2–0 . .	4.47	Normal; *T* upright in all three leads	Reflexes present; moving head; moaning.
	4.50	*R* wave negative in Lead I; rate, 210	Animal is allowed to come out of anesthesia completely.
3–0 and 4–0 . .	4.51 to 4.53	Rate increased, otherwise no change	Eye reflexes abolished; moving head and legs near end of the experiment.
5–0 . .	4.55	Rate, 105; Lead III *T* wave became iso-electric and later partly negative	As above.
6–0 . .	4.58	.....	Anesthesia resumed.
	4.59	Sinus arrhythmia; *T* wave iso-electric	Slightly under; eye reflexes not abolished; anesthesia increased.
7–0 . .	5.00	Lead II *T* wave at first deeply negative, gradually diminishing until flat, then gradually mounting upward higher and higher	Anesthesia continued until deeply under.
7–0 . .	5.02	*T* wave encroached upon *R*, and together they formed a curious bifid oscillation of wide nature; *P*–*R* interval increased gradually and a complete block followed; *R*–*T* combined wave became wider and the voltage lower (arborization type of deflection); no *P* wave was visible, and for a long stretch until death this slow, wide and long ventricular deflection continued	Tongue deeply cyanotic; artificial respiration at 5.01. Animal died.

Résumé. Under light anesthesia the only change noted was in the rate, which increased. Repeating the anesthesia and allowing the animal to recover three times, changes in the direction of the *T* wave occurred. In deep anesthesia marked abnormalities took place in the *R* and *T* deflections, producing a very striking picture. A complete heart-block soon followed and finally the auricular activity ceased altogether and the ventricles continued at a slow rate, with characteristic abnormal complexes, until the death of the animal.

Gilbert,[2] or other unknown factors. What we wish to stress is that in experiments with cats under ether narcosis electrocardiographic changes of varied degrees and types are easily provoked and may readily be mistaken for effect of some drug that may be under investigation.

At the outset of our work we followed the technic of anesthetizing each cat while its electrocardiogram was being taken. Very small

[2] Arch. Int. Med., 1921, **27**, 517; Am. Jour. Physiol., 1921, **56**, 475.

CHART VI.—CAT 145. ELECTROCARDIOGRAM 48 (SEE PRINTS). MAY 3, 1923.

Record No.	Time, P.M.	Electrocardiographic changes.	Anesthesia.
1–0 and 2–0 . .	3.50 to 3.55	Low voltage; *T* wave came off directly from limb of *R* before the base line was reached; deflections were upright in all three leads	No anesthesia.
3–0 . .	4.01	Respiratory variations in rate; lower voltage	Ether for 1 min.; eye reflexes were present; toward end of record additional anesthesia given.
4–0 . .	4.06	Very low voltage in all three leads; sinus arrhythmia	Anesthesia 2 min.; eye reflexes diminished; no anesthesia at end; reflexes returned.
	4.09 to 4.12	No records taken	Ether continued until deeply under.
5–0 . .	4.12	*T* gradually increased in size and finally overshadowed by small *R*; the heart-rate gradually slowed; *T* wave later diminished in size, reaching its previous amplitude	No additional anesthesia; no eye reflexes; Lead II strips recorded 30 sec. apart for 7 times.
	4.14	All deflections regular; later gradually a partial heart-block appeared with the falling-out of a ventricular beat from time to time; *T* wave again resumed the peculiar character as in previous record	Cat still deeply under.
	4.16	2 to 1 heart-block with *R* wave negative during the block period; finally the block became complete 6 to 1, with an abnormal high *R* and a deeply negative *T*; ultimately no ventricular beats occurred and the auricles continued to beat slowly until death	Cat deeply under; a record was taken every 10 sec. for 5 succeeding periods.
	4.22	Cat died	

Résumé. During the light anesthesia only minor changes in the rate of the sinus stimulation were produced. This animal had an abnormal origin of the *T* wave which came directly off the stem of the *R* wave and was rather blunt. Repeating the light anesthesia caused an apparent reduction of the voltage of the *R* wave. During deep anesthesia a series of records showed: At first a remarkable increase in the height of the *T* wave which mounted gradually until it overshadowed the *R* wave. It finally reapproached its former altitude. As the animal became overwhelmingly anesthetized a partial heart-block was induced. This conduction disturbance increased gradually until it finally became complete and the ventricles took on an idioventricular rhythm, having its origin in some infra-auricular foci as shown by the marked abnormality of the deflection. Pre-agonally the ventricles ceased to beat and a slow auricular response continued until death of the animal; the respirations and heart sounds disappeared long before the electrocardiographic oscillations ceased.

TABLE II.—SIX ADDITIONAL EXPERIMENTS CORROBORATING THE EXPERIMENTS WITH ETHER AS TABULATED IN TABLE I.

Ekg. No.	Cat No.	Date, 1922.	Time of electrocardiogram.	Remarks.
1 (0–0) . .	67	May 27	3.00 P.M.	Left ventricular preponderance; rate, 150.
2 (0–0) . .	70	July 12	10.05 A.M. to	Very low voltage in Lead I; average voltage, rate 215 in Leads II and III.
2 (0–1) . .	70	July 12	10.10 A.M.	In Leads II and III rate 215; *T* much more flattened than in Ekg. 0–0 which was of good voltage; almost iso-electric.
3 (0–0) . .	71	July 25	9.40 A.M.	All deflections upright; small voltage and regular rates; each cycle rate 215; *T* very flat.
4 (0–0) . .	73*	Aug. 1	10.26 A.M.	In Lead I low voltage; in Leads II and III fair voltage; *T* down and *P–R* interval equals 0.08 sec.; rate, 250.
4 (0–0) . .	73	Aug. 1	10.31 A.M.	As above.
5 (0–0) . .	75	Aug. 8	9.50 A.M.	Low voltage in Lead I; fair voltage and *T* wave disappeared in Lead II; fair voltage and *T* inverted in Lead III; rate, 215.
6 (0–0) . .	76	Aug. 17	10.32 A.M.	Very low voltage in Lead I; fair voltage, *T* wave flat, rate 215 to 250 in Leads II and III.
6 (0–0) . .	76	Aug. 17	10.40 A.M.	As above; rate, 190.

* Same cat as 71.

TABLE III.—LISTING THE TYPES AND PERCENTAGES OF HEART DISTURBANCES CAUSED BY ETHER NARCOSIS.

Record No.	48	49	13	15	14	50	4	1	2	3	5	6	Total.	Per cent.
Sinus arrhythmia . . .	⊕	..	..	..	..	⊕	..	..	..	..	..	..	2	16.8
Variations in the height of *R* and *S* waves . . .	⊕	..	⊕	..	..	⊕	..	..	..	..	⊕	..	4	33.3
Nodal rhythm	..	⊕	..	⊕	⊕	..	..	..	..	..	..	..	3	25.0
Changes in the direction of *R*	⊕	..	..	⊕	⊕	..	..	..	..	..	..	..	3	25.0
Changes in the direction of *T*	⊕	⊕	⊕	⊕	⊕	⊕	..	..	⊕	..	..	..	7	58.3
Notching of *R* wave . . .	..	..	..	⊕	..	..	..	..	..	..	..	..	1	8.3
Increase in the *P–R* interval	..	⊕	..	⊕	..	..	..	..	..	..	..	..	2	16.8
Partial heart-block . . .	⊕	..	..	⊕	⊕	..	..	..	..	..	..	..	3	33.3
Complete heart-block . .	⊕	⊕	..	⊕	..	..	..	..	..	..	..	..	3	33.3
Ventricular extrasystoles .	..	..	..	..	..	⊕	..	..	..	..	..	..	1	8.3
Auricular fibrillation . .	..	..	..	..	⊕	..	..	..	..	..	..	..	1	8.3
Auricular flutter	..	..	..	⊕	..	..	..	..	..	..	..	..	1	8.3
Number of disturbances .	6	4	2	8	5	4	0	0	1	0	1	0	31	

TABLE IV.—ETHER ANESTHESIA.

Cat No.	Ekg No.	Degree.	Duration.	Electrocardiographic changes.
99	13	Cat rapidly brought into deep narcosis and gradually allowed to recover to normal state	3.50 to 4.16 P.M. (26 min.)	7 electrocardiographs taken; there were no definite changes, except for slight variations in the height of *R* and *S*.
100	14	.....	4.20 P.M. (ether begun)	7 electrocardiographs taken; under deep anesthesia there developed a high-grade heart-block; as recovery took place a partial heart-block appeared and soon thereafter a normal rhythm interrupted by occasional extrasystoles (see prints and full protocol).
		Deeply narcotized; gradually allowed to recover out of ether	4.31 P.M. 4.50 P.M.	
101	15	Received ether in varying concentrations; deeply narcotized	Over period of 17 min.	Earliest changes were low voltage in Leads I, II and III, under moderate anesthesia; bradycardia; *P–R* interval increased to 0.20 sec.; in Lead I *P* wave disappeared; *R* deflections were inverted, joining *T* wave.
		Deeply anesthetized continued	6 min.	Auricular flutter; *R* wave widened and joined to *T*.
			2 min. (longer)	Slow ventricular rhythm; no *P* wave; *R* and *T* diaphasic.
			8 min. (longer)	Diaphasic deflections more pronounced; occasional *P* wave observed.
			10 min. (longer)	*R* and *T* complex very wide and notched; occasional *P* wave.
			(Death of cat)	Finally small irregular oscillations at more rapid rate, with occasional diphasic deflections until heart's standstill.
145	48	Light anesthesia	4.00 to 4.01 P.M. (1 min.)	No abnormalities.
		Light anesthesia	4.05 to 4.07 P.M. (2 min.)	Low voltage in Lead I.
		Moderate anesthesia	4.09 to 4.12 P.M. (3 min.)	Very low voltage in all three leads; large *T* deflections with changes in height of *T*; in Lead III *T* and *R* united and assumed a diphasic character.
		Deep anesthesia	4.14 to 4.16 P.M. (2 min.)	All deflections variable; partial heart-block (2 to 1) which soon became complete; died suddenly.
146	49	Light anesthesia	2 min.	No effect.
		Light anesthesia	4.15 to 4.47 P.M. (2 min.)	No effect.
		Light anesthesia	4.50 to 4.55 P.M. (4 min.)	Leads I, II and III slow rate; *T* inverted in Lead III.
		Moderate anesthesia	4.55 to 4.59 P.M. (4 min.)	Sinus arrhythmia.
		Deep anesthesia	5.00 to 5.02 P.M. (4 min.) (Died rather suddenly shortly after)	*R–T* assumed diphasic character; *P–R* interval increased.

TABLE IV.—ETHER ANESTHESIA.—(*Continued.*)

Cat No.	Ekg No.	Degree.	Duration.	Electrocardiographic changes.
147	50	Very light anesthesia	3.31 to 3.33 P.M. (2 min.)	Lead I very low voltage (electrocardiograms normal without ether).
		Very light anesthesia	3.34 to 3.35 P.M. (1 min.)	Lead I low voltage.
		Slightly deeper anesthesia	4.12 P.M.	Lead I alternating ventricular extrasystoles.
		Very light anesthesia	Until 4.25 P.M. (had been given practically continuously for 50 min.)	Lead II, *T* diaphasic; 4.25 P.M., Lead I showed extrasystoles and low voltage (see prints); alternating extrasystoles, tachycardia; *T* inverted.
		Deep anesthesia	4.30 to 4.40 P.M. (2 min.)	No effect, that is, normal electrocardiograms.
		Recovered from anesthesia	4.45 P.M.	
			OUABAINIZED CATS.	
67	..	Light anesthesia	3 min.	Left ventricular preponderance; rate, 150.
70	..	Light anesthesia	10 to 10.05 P.M.	Lead I very low voltage; rate, 215; Leads II and III, *T* wave flattened, almost iso-electric.
71	..	Light anesthesia	.....	All deflections upright; small voltage; rate, 215; *T* very flat.
73	..	Light anesthesia	5 min.	Lead I low voltage; *P* and *R* increased 0.08 sec.; rate, 250.
75	..	Light anesthesia	6 min.	Lead I low voltage; Lead II, *T* not visible; Lead III, *T* inverted; rate, 215.
76	..	Light anesthesia	8 min.	Lead I low voltage; Leads II and III fair voltage; *T* flat; rate, 215 to 250.

NOTE.—This table is a compilation of the electrocardiographic changes encountered in the cats studied for the effects of ether upon their hearts.

amounts of ether were given by the open-cone method, with carto secure a very "light anesthesia" and to permit the cat "to come out" just as soon as the electrocardiographic records were finished. We feel, therefore, that very small amounts of ether used as an anese thetic in cats probably cause only the slight effects as described. Nevertheless, in a group of animals, one of whose series of electrocardiograms we print, it will be noted that this ouabainized animal shows nodal rhythm in its electrocardiograms while under the influence of small amounts of ether anesthetic used solely to keep the animal quiet for a very short time (Ekg. 12). The condition of nodal rhythm promptly disappeared when the ether anesthetic was removed, though ouabain was still in the animal and supposedly undestroyed. This experiment, as well as the results obtained in our study of the effects of ether alone upon the cat's heart, point to the possibility of a summated effect when ouabain

and ether are used in the same animal at the same time. This inference is not without interest in a consideration of the clinical habit of "digitalizing" patients directly before operation carried out under ether narcosis. The investigations of Lenox, Graves and Levine[3] seem clear as to the effects of ether upon the human heart and our animal studies are in accord with their observations. It may not be amiss to emphasize that ether anesthesia, clinically, is administered in an inaccurate, unquantitative manner, and that as a consequence, though its effect upon the heart is striking under adequate ether inhalations, the threshold dose at which these effects appear must be uncertain and variable. The exhibition of nodal rhythm, for instance, in a cat's heart may be interpreted as a "spontaneous" normal phenomenon if it occurs in the unanesthetized animal. Despite the fact that small doses of ether seem to cause little change in the heart, disturbances so comparatively moderate as nodal rhythm and changes in the direction of the *T* wave may indicate an ether response rather than an intrinsic heart derangement, since the threshold dose for cardiac change from ether is so variable. In other words, a heart disturbance, however slight, may perhaps be caused by ether inhalation however "light" the anesthesia may seem to be. To mention but a few inconstant factors bearing upon this point, we have the amount of ether used, the degree of ether concentration, the duration of the narcosis and the general pharmacological effect of ether as distinct and a part from the direct effect of ether upon the living heart.

In six other experiments cats received ether as a brief narcotic in order to permit the taking of electrocardiographic tracings while these animals were ouabainized. Though ether effects were not studied here as a primary interest, nevertheless, our distinct impression is that here also the electrocardiographic changes from ether narcosis were similar to those detailed above. Table II indicates these results.

Conclusions. 1. Cardiac abnormalities occur promptly upon adequate changes in depth and duration of ether anesthesia.

2. These irregularities are transient and go hand-in-hand with the depth and duration of the anesthetic. Upon recovery from ether narcosis, no matter how deep, the cat's heart resumes its normal characteristics; all cardiac irregularities, striking and alarming as they may be, disappear rapidly.

3. No summated or cumulative effects are apparent.

4. Heart abnormalities appear under moderate and, nearly always, under deep ether anesthesia. As a rule, a very light anesthesia, whether brief or prolonged (forty minutes or more) causes little if any changes in the electrocardiograms. The changes appear if sufficient ether is administered, and disappear promptly

[3] Arch. Int. Med., 1922, **30**, 57.

when ether inhalation is discontinued. This is so whether we start with a "light anesthesia" or a "deep anesthesia," or whether we alternate light and deep anesthesia.

5. The irregularities encountered assume many types and degrees of abnormalities. On many occasions the effects resemble, strikingly, those produced by digitalis intoxication.

THE PATHOLOGY OF FATAL MEASLES.

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During the months of November and December, 1923, an epidemic of measles occurred in Panama and numerous patients were admitted to the Hospital Santo Tomas. Many of the cases were severe and 11 ended fatally. Autopsies were done in all fatal cases. In 8 of the autopsies death was due to bronchopneumonia differing in no important particular from the bronchopneumonia often observed after measles. In 3 cases death occurred so soon that bronchopneumonia of any important extent had not yet developed. From observation of the patients, from the circumstances under which they died, and from the pathological changes found, it is believed that the deaths were due to uncomplicated measles and that the lesions found are the lesions of the disease. As a fatal termination in measles during the first few hours after the appearance of the exanthem is unusual, and as the clinical symptoms point so sharply to the location of the lesions in the bronchi, brief histories of the cases are given.

Case Reports. Case I.—A. A. (Autopsy No. 8017), a female, aged twelve years, was admitted November 24, 1923, and died the next day. Death occurred three hours after the appearance of the rash.

Clinical Résumé. The patient gave no history of previous illness or of having had the usual diseases of childhood. She was admitted on the third day of illness with these symptoms: Fever, temperature 104° F., headache, coryza, conjunctivitis, and cough. The skin was hot and dry and markedly hyperemic, the lips and finger nails cyanotic, the conjunctivæ injected, with small hemorrhages into the scleræ. The mouth and throat were red; there was no membrane on the tonsils. Koplik's spots were present. Respirations were rapid and shallow and there was a slight dry cough. Expansion was equal but somewhat restricted on both sides. The percussion

note was hyperresonant over the whole chest, there were no areas of decreased resonance, no modification of voice sounds. Inspiration was harsh and short, expiration harsh, and there were numerous musical rales over the whole chest. The heart was not enlarged, the rate was fast and slightly irregular, the pulse small. The liver and spleen were not palpable. Blood—no malaria parasites. Leukocytes 12,000. The urine showed a trace of albumin, no casts.

On the evening of admission the patient had the appearance of having severe bronchitis, except for the marked hyperemia of the skin and the cyanosis. No definite pneumonic signs were noted.

FIG. 1.—Photomicrograph of section of buccal mucous membrane, Case No. 8017, ×200. Focal necroses in the epithelium with reaction in the papillary vessels.

The following morning the general cutaneous hyperemia cleared away and a bright measles rash appeared. The respiration and heart action became faster and at noon the pulse was imperceptible. Exitus 1.20 P.M.

Autopsy Protocol. Autopsy a few minutes postmortem.

Anatomical Diagnoses. Measles (exanthem); catarrhal tracheitis; capillary bronchitis; lymphadenitis (cervical and mediastinal).

The body is that of a well-developed and well-nourished girl about twelve years of age. There is a well-marked, red, macular rash on the face, neck, upper trunk and over the upper arms. The conjunctivæ are pinkish-red and a small amount of exudate is

adherent to the margins of the lids. A few small, indefinite, gray spots can be seen on the buccal mucous membrane. Ventral incision: The fat is normal in amount, the muscle is dark red. No localized areas of loss of color can be seen in the muscle and no hemorrhages into the subcutaneous tissues can be found. Both pleural cavities are free from fluid and adhesions. The thymus is normal. The right lung is increased in volume and almost fills the right pleural cavity. The consistence is slightly increased,

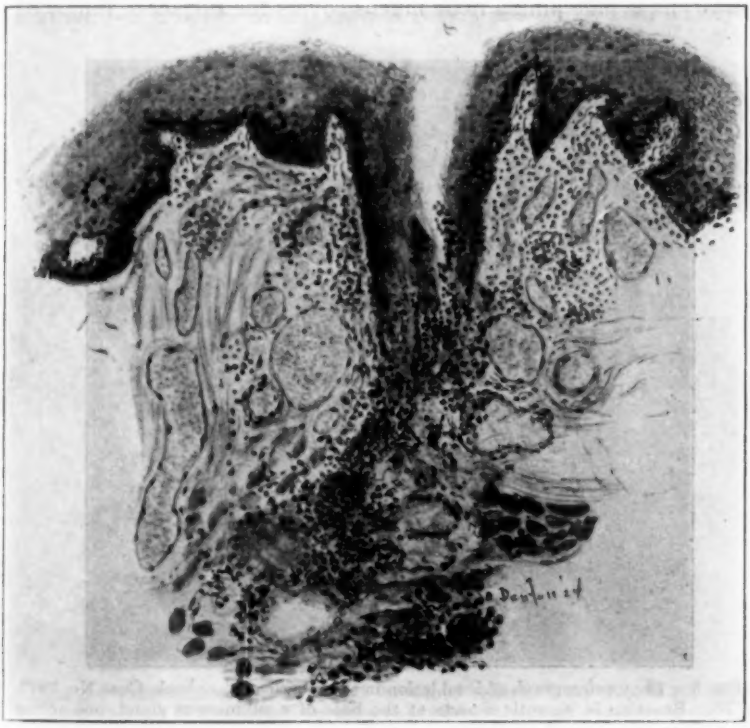

FIG. 2.—Drawing of a submucous gland from the mouth, Case No. 7976, ×100. Koplik spot. Suppurative reaction in and about a gland and duct from the cheek. Note the collar-like plexus of veins about the duct. Grossly this lesion was less than 1 mm. in diameter.

the weight but little increased. The pleural surfaces are smooth and pinkish-gray except for small (pin-head sized) hemorrhages beneath the pleura. In the lower lobe there are several small, slightly depressed dark red, firm, wedge-shaped areas, none more than a centimeter in area (small atelectases). There is no fibrin on the surface. On section the cut-surface is mottled in pinkish-red and red, the mottling being due to roughly circular dark red areas about bronchial radicles of various sizes. About some of the larger

bronchi some of these have a faint gray tint. There are numerous small hemorrhages into the peripheral parenchyma. An occasional small bronchiole contains a drop of white pus. When thin slices of lung are placed in fixing fluid (Zenker's) small clusters of opaque yellow appear about bronchioles. These areas were dark red and quite translucent before fixation. The left lung is like the right. Some bronchi contain a small amount of thin white pus. The mucous membrane is pinkish-red with a few small gray flecks on the surface of some of the larger branches. The mucous membrane of the larynx is pale pink a little mucus covers the surface. Followed

FIG. 3.—Photomicrograph of focal lesion in the muscle of the cheek, Case No. 7976, ×175. Reaction in necrotic muscle at the base of a submucous gland, one acinus and a thrombosed vessel are shown.

downward the mucous membrane of the trachea becomes redder and there is more mucus on the surface. The cervical and mediastinal lymph nodes are enlarged and pinkish-gray on section. The heart is of normal size. Both auricles are slightly dilated. The valves and valve orifices appear normal. The heart muscle is dark bluish-red in color, and softer than normal. The spleen is not enlarged and is of normal consistency. On section the cut-surface is purplish-red, the follicles are small and numerous and readily visible. The liver is of normal size and brownish-red in color. Several small, light yellow ischemic areas are present

in the margins. The cut-surface is brownish-red and slightly opaque but lobular markings are visible. The kidneys are of normal size and pale red in color. On section they have normal markings. The adrenals are of normal size and normally pigmented. No hemorrhages are present in the parenchyma. The mucous membrane of the bladder is pale pink except over the trigone where it is slightly injected. No hemorrhages are present. The mucous membrane of the stomach and intestine is of normal color. No hemorrhages are present in the mucosa. The skull and scalp are normal. The bones of the cranial cavity are bluish-gray in color;

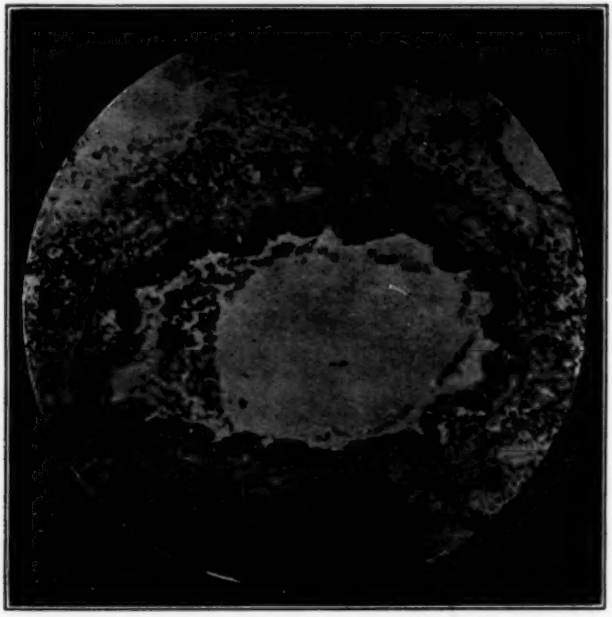

FIG. 4.—Photomicrograph of small bronchial radicle, Case No. 8017, ×700. Vacuolar changes in epithelium, purulent exudate in the lumen, reaction in the wall, beginning reaction in surrounding alveoli.

the blood spaces in the cut edge of the skull cap are bluish-red. The brain is pale and everywhere the cerebral markings are very much flattened out. The pia-arachnoid contains no visible fluid, the sulci are shallow, the gyri are wide and flat. The vessels of the cortex are not prominent. The cerebral veins of the base are filled with blood.

CASE II.—I. N. (Autopsy No. 7976), a female, aged six years, was admitted November 4, 1923 and died November 8, 1923. Death occurred eighteen hours after the appearance of the rash.

Clinical Résumé. No details were available as to past history. Her symptoms on admission were: Fever, temperature 104° F., coryza, conjunctivitis and slight cough. A sister one year older was admitted the same day with similar symptoms. Examination showed a well-developed and well-nourished female child with pharynx slightly injected, conjunctivæ red. There was a thin serous discharge from the nose, and respirations were fast and noisy. There were no areas of dulness; the percussion note slightly hyperresonant over the whole chest, with a few scattered rales. November 6: Her temperature was 104°, with slight cyanosis of lips and

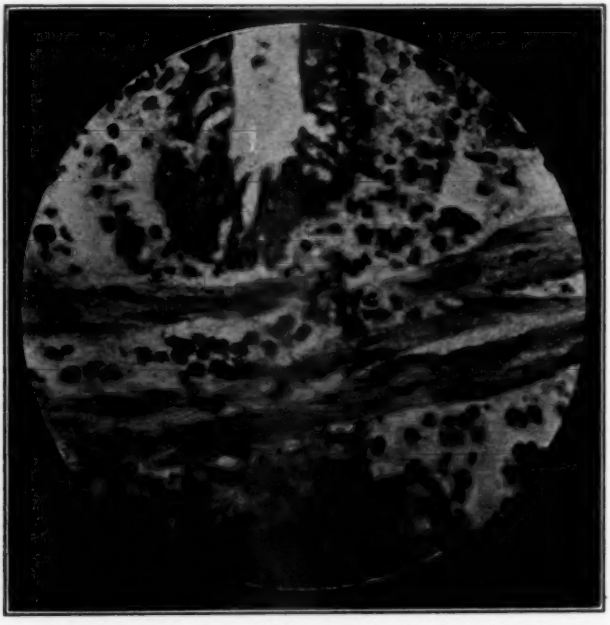

FIG. 5.—Photomicrograph of bronchiole, Case No. 8017. ×700. Vacuolar changes in the epithelium, endothelial and polymorphonuclear leukocytes in the epithelium and submucosa. Phagocytosis of necrotic smooth muscle in the wall.

fingernails, but no dulness. A typical measles rash appeared on the patient's sister, admitted the same day. On November 7, a typical measles rash appeared on the patient with but little change in the physical signs. Exitus November 8, 1923.

Autopsy Protocol. Autopsy a few minutes postmortem.

Anatomical Diagnoses. Measles (exanthem); bronchopneumonia (early); catarrhal tracheitis; capillary bronchitis; lymphadenitis (cervical and mediastinal).

The body is that of a well-developed and well-nourished female child about six years of age. There is an extensive papular rash

over the face, chest and upper arms. On the face the papules are very readily palpable. In the ventral incision, the fat and muscle are normal in amount and color. No hemorrhages are visible in the soft tissues. Both pleural cavities are free from fluid and adhesions. The whole left lung is increased in volume. The pleural surfaces are smooth and mottled in red and faint gray. The lymphatics beneath the pleura are prominent as gray lines. The cut-surface is mottled in red and faint gray; the gray areas are in the form of indistinct rings and clusters about small bronchial radicles. Very little exudate comes off the cut-surface, a few small

FIG. 6.—Camera lucida drawing of a section of a small bronchial radicle, Case No. 8017, ×900. Small single and paired bacilli within leukocytes in the lumen and in the submucosa.

beads of pus appear on slight pressure. The lower lobe is somewhat firmer than the rest of the lung and the gray areas about some of the bronchi are more distinct. The right lung is like the left. The bronchial mucous membrane is covered with mucopurulent material and on removing this the mucous membrane is rose-red in color. The larynx and trachea contain mucopurulent exudate, the mucous membrane is injected throughout. The lymph nodes of the neck and mediastinum are enlarged, pinkish-gray and rather soft in consistence. No changes are visible in the remaining organs.

CASE III.—G. L., (Autopsy No. 7997). A female, aged one month and twenty days, was admitted November 22, 1923, and died the next day, twenty-four hours after the appearance of the rash.

Clinical Résumé. The child was brought to the hospital suffering with rapid breathing, coryza, conjunctivitis and a recent, typical measles rash. Two other children from the same family and living in the same rooms were admitted a few days previously with measles. No definite physical signs were noted in the child's chest on admission. During the night the respirations became more rapid; exitus occurred eight hours after admission.

Autopsy Protocol. Autopsy one hour postmortem.

Anatomical Diagnoses. Catarrhal tracheitis; bronchopneumonia (early); capillary bronchitis; lymphadenitis (cervical and mediastinal).

The body is that of a well-developed and well-nourished female child about two months old. The skin of the face, chest, shoulders and upper arms contains numerous small, red macules and indistinct papules which in places are confluent. No gross lesions in the buccal mucous membrane are seen. In the ventral incision the fat and muscle appear normal. There are no hemorrhages in the subcutaneous tissues. No fluid is present in the pleural cavities. Both lungs have the same appearance; their volume is slightly increased. There is no fibrin on the pleural surfaces. Underneath the pleuræ there are numerous, small, red points of hemorrhage. The consistence is slightly firmer than normal. On section the cut-sursaces are mottled in red and pinkish-red. Very indistinct gray areas are visible about some of the larger bronchi. An occasional bronchiole contains a small drop of pus. A section down through the trachea and bronchi shows a uniformly red mucous membrane covered in places with scanty, mucopurulent exudate. The lymph nodes in the neck and at the bifurcation of the trachea are enlarged and pinkish-gray on section. The other organs show no significant changes.

From a clinical point of view these cases are very similar to other cases observed during the epidemic. The symptoms and physical signs observed in these cases were also noted in cases which terminnated in recovery. They indicate primarily interference with respiration and accumulation of carbon dioxide in the blood.

Histological Examination of Tissues. No changes referable to measles have been found in any organs except the skin, mouth, pharynx, trachea, bronchi and lungs. The changes in the respiratory tract are very similar in the three cases, the variations being very slight and simply a matter of degree. A careful search has been made in sections of numerous simple tissues for disseminated vascular lesions such as one would suspect if the virus of the disease circulates in the blood. No lesions of this type have been found.

The Skin. The changes in the skin agree with the accounts

of the skin lesions given by Ewing[1] and later by Mallory;[2] the lesions consist in moderate hyperemia and edema of the corium with degenerative changes in the epidermal cells. The endothelium of the capillary and precapillary vessels of the corium show rather marked swelling and proliferative reaction. Mitoses in capillary endothelium and in that lining small veins are fairly numerous in the early hours of the rash. Accumulation and proliferation of endothelial leukocytes about the vessels are more prominent in the second and third days of the rash. From study of the skin obtained at autopsy and excised during life in numerous cases it seems very clear that the changes in the epidermis are secondary to those in the capillary and vascular endothelium. The skin lesions do not show any evidence of being infectious in nature, beyond the proliferative activity on the part of the endothelium. Thrombi have never been found in the specimens examined. Very similar changes have been observed in toxic rashes which obviously had no relation to measles. Various, small, globoid and rod-like bodies have been seen within the endothelial cells and about the bases of cells of the basal layer, but none of them have had sufficiently definite morphological characters to warrant regarding them as microörganisms. Bodies of the type described by Mallory[2] have been observed, but is impossible to add more than conjecture as to their nature. All these things seen in the skin have been more numerous in the second and third days of the rash.

Mouth and Pharynx. There are three types of lesions in the mouth and pharynx. (1) Small collections of endothelial and polymorphonuclear leucocytes in small necroses of the epithelium. Beneath these necroses there is reaction in the endothelium of the papillary vessels. They appear to start in the epithelium and later, sloughing causes the formation of a small ulcer. (2) Suppurative lesions of small submucous glands and their ducts. (3) Inflammatory lesions of small submucous lymph follicles. The second lesion is of interest for two reasons. The typical Koplik spot is surrounded by bluish and red zones. From the comparative constancy in location of the Koplik spot it seems clear that it must originate in a rather constant anatomical structure. For this reason and on account of its size there is little question that it originates in a submucous gland. The ducts of each one of these glands is surrounded by a collar of dilated veins and these offer ready explanation of the bluish halo about the spot. Most of the focal lesions found in the buccal mucous membrane are so small that they would hardly be grossly visible at the time of or before the appearance of the exanthem. Some lesions found several days after the appearance of the rash are large enough to be seen with the unaided eye. The suppurative reaction in the glands frequently extends beyond the limits of the glands and leukocytes accumulate about the margins. In Case II there is reaction in necrotic muscle of the cheek with

thrombosis of small vessels, which is interesting on account of its obvious relation to noma. Noma, by the way did as a matter of fact, cause the death of two children in the epidemic from which this material was gathered. Lesions have not been found in the buccal mucous membrane which give any evidence of being due to a blood-borne virus. All those found appear to be due to extension from the mucous surface. No sections have been made from the lips and gums and it is therefore impossible to express an opinion as to the presence of herpetic lesions there.

Larynx and Trachea. Throughout the larynx and trachea the mucous membrane is edematous and groups of superficial cells and solitary deeper cells are undergoing degenerative and vacuolar changes. The vessels of the stroma and submucous tissue are dilated, the endothelial cells are large and many are undergoing cell division. About the vessels and in the stroma are large numbers of endothelial leukocytes, plasma cells, lymphocytes and small numbers of polymorphonuclear leukocytes. This increase in cell elements is partly due to inflammatory reaction and partly to increase in size and number of cells of the lymphoid stroma of the upper respiratory tract. The ducts of submucous glands are filled with desquamated epithelium and leukocytes. The acini of many glands contain leukocytes and countless numbers of a small, Gram-negative bacillus. These organisms are also present in numbers in the perinuclear vacuoles of epithelial cells. Other bacteria are very few in number. In the stroma about many of the submucous glands are areas of reaction with endothelial and polymorphnuclear leukocytes. The lymph nodes at the lower end of the trachea show marked inflammatory changes. The sinuses contain large numbers of plasma cells, large phagocytic cells and small numbers of polymorphonuclear leukocytes. The endothelial cells lining the sinuses are large and often contain mitotic figures.

The epithelium of the trachea is everywhere intact, degeneration of epithelial cells being limited to solitary cells and small groups of superficial cells. Active regeneration of epithelial cells is evident by the numbers of mitotic figures in dividing cells. The changes in the stroma are more marked than those in the epithelium as the reaction must necessarily take place from back of the epithelium. In general the inflammatory reaction is much more mild than in the cases described by Ewing.[1]

Bronchi. The changes in the bronchi are much like those in the trachea but complicated, in places, by rather extensive destruction of epithelium. Here again the lesions are primarily in the epithelium, but reaction can only take place from the back. In the larger bronchi the epithelium is thicker than normal and there are more layers of cells than normal. The epithelium is generally intact, only individual cells undergoing vacuolar degeneration with the formation of small, clear spaces in the epithelium. Neighboring cells may be

well preserved, oversized or dark-staining with mitotic figures and atypically arranged chromatin. In the small cavities left by degenerating epithelial cells are small groups of two or more leukocytes and straggling ones between the epithelial cells. On the surface there is in places a small amount of purulent exudate and small masses of mucus, but no fibrin. Both the leukocytes and mucus contain numbers of this same small bacillus. Practically no other organisms are present. The walls of bronchi are considerably thickened by dilated vessels lined with large endothelial cells and by numbers of endothelial leukocytes, plasma cells, lymphocytes and small numbers of polymorphnuclear leukocytes. Small veins and lymphatics often contain numbers of large mononuclear cells and fibrin, but no thrombi.

In the smaller bronchial radicles the epithelium is not generally necrotic but in places is raised off the connective tissue backing with endothelial leukocytes and pus cells beneath it. Long tags of well-preserved epithelium, detached from bronchial walls lie in open spaces surrounded by leukocytes.

In many bronchioles the wall cannot be made out, for it often shades off into swollen, contiguous alveolar walls. In places, alveoli close to bronchial radicles contain large mononuclear cells from the respiratory epithelium and fused sheets of atypical respiratory epithelium. Numerous giant cells with five to twenty nuclei and well preserved or degenerating cell bodies are present. A group of alveoli close by may contain pus cells and erythrocytes with but little or no fibrin. Dark-staining compact masses of polylobate nuclei, between which no cell boundaries can be seen lie in some alveolar spaces. In numerous alveoli and infundibula the exudate has the appearance of having been aspirated. Purulent exudate and short cylinders of infundibular epithelium lie in spaces where the respiratory epithelium and bronchiole show no reaction.

It was anticipated that some of the dark-red areas seen grossly would have some relation to small arteries of the lung and that changes in the precapillary vessels more or less analogous to the changes in the cutaneous vessels would be found but this relationship has not been established. The areas of reaction in the lung are purely peribronchial in distribution and the only vascular lesions found have been in the small vessels beneath the epithelium in the bronchi and in small veins in the septa draining penumonic areas.

The actual extent of the bronchopneumonia is limited and the primary injury to the lung is apparently not very severe. The reaction, except in areas where the exudate has pretty definitely been aspirated, is mononuclear in type and made up of endothelial leukocytes, lymphocytes and large phagocytic cells from the respiratory epithelium. The sheets of fused epithelial cells and the formation of large giant cells represent a process of some days' duration and imply a rather weak injurious agent.

There seems to be no question that the organism found in this material is responsible for the lesions present a few hours after the appearance of the exanthem. This influenza-like organism is readily distinguished from Gram-positive organisms, such as pneumococci and streptococci, by the use of Goodpasture's stain as modified by MacCallum. The staining reaction of the organism is somewhat different from Gram-positive organisms in Giemsa preparations. The absence of other organisms in the lesions is additional good evidence of the importance of this organism in the lesions.

The eight cases in which death resulted from pneumonia later (six to twenty days after the rash) are entirely comparable to the cases described by MacCallum.[3] In these cases Gram-positive organisms are demonstrable in the tissues and the Gram-negative bacilli are still present in some of them. The term interstitial bronchopneumonia very aptly describes the pneumonia in the later cases and it is a very logical result of the lesions found in the earlier cases. Post-measles pneumonia cannot be regarded as an accidental complication of measles but, the extension of a process well started when the exanthem appears. Reaction in the bronchial walls, which in many situations implies also reaction in the framework of the lung, is the only way in which reaction can take place in inflammation of the broncial mucosa. The transportation of the organism found in these cases from the mucous membrane along septal veins and lymphatics readily explains the interstitial location of some of the lesions found in later cases as Gram-positive organisms would be transported along the same paths.

The lesions in the trachea and bronchi are very similar to but less intense than those described by Ewing and it would be difficult from a study of the cases to come to any other conclusion than that arrived at by him, namely, that there exists in measles, "infection by a rapidly multiplying microörganism of the class of bacteria." Clinically the changes in the respiratory tract give good evidence of their existence four or five days before the exanthem. The pathological changes are confined to the respiratory tract and largely to the epithelium and they indicate that the morbid process is located there.

Summary and Conclusions. (1) In these 11 postmortems on subjects dead of measles, death was due in all probability, in 3 cases to the virus of measles.

2. The primary lesions of measles are located in the lower trachea, bronchi and contiguous lung.

3. There are three types of lesions in the buccal mucous membrane: (*a*) Reaction in focal necroses in buccal epithelium; (*b*) suppurative lesions in and about submucous glands and their ducts; (*c*) inflammatory lesions of submucous lymph follicles.

4. The Koplik's spot is an inflammatory lesion of a submucous

gland and the bluish halo about it is due to the collar-like plexus of venules about the duct.

5. The Gram-negative bacillus found in the lesions in these three cases has every appearance of having etiological relationship to measles and deserves further investigation.

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RETROPHARYNGEAL LYMPHADENITIS IN INFANCY AND EARLY CHILDHOOD.

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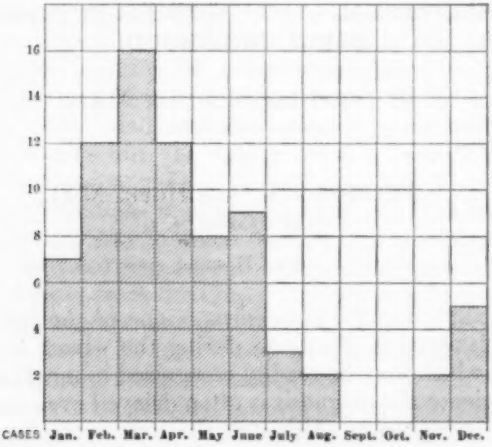
Retropharyngeal lymphadenitis is one of the frequent causes of the hospitalization of infants during the winter months. It is a condition which may be readily recognized in most instances, but in our experience the diagnosis is often delayed even until the onset of alarming symptoms. Although the term retropharyngeal swelling unfortunately seems to convey the loosely applied meaning of abscess, it is reasonable to suppose that the retropharyngeal lymph glands may become infected and enlarge as frequently as the glands of the cervical chain, suppurating in only a small percentage of cases, as do the cervical glands. Judging by the mild symptoms in some cases of retropharyngeal lymphadenitis seen by us, it may be inferred that the condition occurs with greater frequency than is believed.

For a complete study of the etiology, anatomy and pathology of the condition, with a survey of the literature, the reader is referred to an excellent article by Frank.[1] A study of the following 77 records of infants and young children with retropharyngeal swelling admitted to the wards and out-patient service of the Babies' Hospital during the past ten years seems to yield data of sufficient interest to merit publication.

The youngest case occurred in an infant, aged two months, and the oldest in a child aged four years. Twenty-three of the cases were in infants not over six months of age, and 19 between the

ages of six and nine months. Fifty-five cases, or 71 per cent, were not over twelve months of age, which corresponds with the age incidence given by both Bokai[2] and Holt and Howland.[3] That even very young infants do not escape the disease is proved by its occurrence in 4 cases not over four months of age.

As noted in the accompanying chart the prevalence of retropharyngeal lymphadenitis follows closely the curve of the respiratory infections, being highest in the late winter and spring with an abrupt decline at the approach of summer. Season, however, does not entirely exclude the possibility of the disease, as shown by the appearance of several cases in June and a few in July and August. (See Chart.)



Seasonal incidence of retropharyngeal lymphadenitis.

Although the average child admitted to the wards of the Babies' Hospital is undernourished and underdeveloped, and generally has a history of difficult digestion, poor hygiene and neglect, the cases of retropharyngeal lymphadenitis seemed to be exceptions to this general classification, as will be noted in the following: Among 58 cases, in which there were careful notes by the examining physician regarding the nutrition of the child at the time of admission, 48, or 83 per cent, were described as well nourished, and the balance showed varying degrees of malnutrition. It seems fair to assume that a rhinopharyngitis must have preceded the involvement of the lymph nodes in the majority of cases, yet the inference may be drawn that it is not usually of great severity, as in only 9 of the patients admitted had this been sufficiently marked to impress the family with its importance as a possible etiological factor. The presumption is that retropharyngeal lymphadenitis may occur with equal frequency as a complication of a mild or a severe upper respi-

ratory infection. The symptoms which impressed the parents of 40 of the patients as being sufficiently grave to warrant hospital relief, were some deviation from normal respiration. In most of this group it was described as "difficult breathing," in a few as "noisy breathing," in one "harsh breathing" and one parent stated that the child had become "short-winded." Of the 77 cases, in only 4 was the sole complaint "difficulty in swallowing," while 2 of the 40 cases previously mentioned had difficult deglutition in addition to respiratory difficulty. Frank makes the observation, which has also been noted by others, that when the swelling is high in the pharyngeal wall there is no interference with respiration, but difficulty with deglutition is usually noted. If the swelling is low in the throat the respiratory difficulty becomes prominent. He quotes Symington, who observed that, though the neck as a whole is relatively longer in children than in adults, the larynx in infancy is fully one vertebra higher in position.

In 25 of the patients swelling of the neck had been noted by the parents as a precursor of difficult deglutition or embarrassment of respiration, or had appeared coincidently, or was the only symptom observed. The appearance of swelling of the neck, due to cervical adenitis, in 1 of every 3 patients draws attention to the importance of carefully excluding an associated retropharyngeal lymphadenitis in every child with cervical lymphadenitis. On admission to the hospital, 56, or 73 per cent, of the cases had cervical lymphadenitis. In 27 of these the swelling was bilateral, and in several it was very extensive. As a commentary on the chances of liquefaction of the glands, and this would seem to hold good for either cervical or retropharyngeal glands, in only 4 of the group of 56 with cervical adenitis did demonstrable liquefaction of the cervical glands occur. In other words, the chances of glands in that region suppurating after infection is apparently only 7 per cent.

It would seem when with upper respiratory infections one gland becomes infected, there is apt to be a reaction of the neighboring lymph glands.

As further evidence of this, the figures for involvement of the tonsils may have a bearing. Among 45 cases in which a careful examination of the tonsils was made at the time of admission, 35, or 77 per cent, were enlarged. Of the remaining 10 cases, 4 had had tonsillectomies, 2 were described as congested and the balance were normal. There was no variation between the frequency of involvement of the right and left side of the retropharynx. In 1 case the swelling involved both sides of the pharynx, probably as a result of infection of several retropharyngeal glands. In 3 cases the swelling seemed to be directly in the midline.

The extent of the temperature reaction is apparently not a guide to the severity of the symptoms, as only 27 of the cases had a temperature above 100° F., and of these but 14 were 103° F. or above.

The blood picture showed a reaction out of all proportion to the rhinopharyngitis, which usually precedes and accompanies the disease. The leukocyte reaction, however, could not be used as an aid in differentiating the stages of infective lymphadenitis, that is, before or after suppuration, as the total counts in some of the former were as high as in the latter. In 35 cases of retropharyngeal lymphadenitis, in which leukocyte and differential counts were made, the average was 20,700 per c.mm., with a polymorphonuclear neutrophile average of 68 per cent, as contrasted with 18 unselected cases of simple uncomplicated rhinopharyngitis or rhinitis, in which the average leukocyte count was 12,900 and the average of polymorphonuclears was 50 per cent.

As mentioned previously, the number of lymphadenitis cases in our collection which proceeded to suppuration can hardly represent or be taken as an index of the frequency of suppuration in infective retropharyngeal lymphadenitis, since it is our belief that many cases of simple lymphadenitis retrogress spontaneously, unrecognized as such. The recorded cases with severe symptoms, most of which suppurated and were hospitalized for that reason, therefore give us no data as to the frequency of suppuration. However, of 74 cases on which records are available, in 7 or 9.5 per cent the retropharyngeal lymphadenitis subsided spontaneously without treatment, and these 7 patients were discharged either improved or cured of the condition for which they were admitted. The infants of this group were from two to twelve months of age. This is of special interest, as it demonstrates that the aforementioned glands may resolve at any age of infancy. It also suggests the advisability of delaying surgical interference in all cases until there is a certainty of suppuration and ample opportunity is allowed for the glands to resolve. The following history illustrates this type of case.

Case Reports. M. M., a nursing infant, aged five months, was admitted to the Babies' Hospital, March 25, 1918. The chief complaint was "inability to swallow." One week prior to admission it was noted that the infant had "difficulty in nursing." "Whenever she attempts to nurse she strangles, and is unable to swallow the milk." She was very hungry during the entire week, there was no vomiting, starvation stools were observed, scanty urine and a weight loss of 2 pounds. Fever had not been noted. The physical examination showed a moderately well-nourished infant, who appeared acutely ill. Retraction of the neck, and a hoarse cry was noted. A mucopurulent discharge from both nostrils was present; the tonsils were congested and slightly enlarged. The pharyngeal wall on the right side was thickened and indurated with moderate bulging into the pharynx. A large amount of adenoid tissue was present. In attempting gastric gavage by the nasal route it was found impossible to pass the stomach tube

through the right nostril, and with difficulty it was passed through the left. To combat the dehydration frequent hypodermoclyses were given, and gastric gavage was continued for several days The stools shortly became fecal in character, the hoarseness disappeared, the swelling in the right pharyngeal wall gradually subsided, but could still be felt seven days after admission. The temperature at the time of admission was 102.5° F.; it rapidly subsided however, and five days later the patient became afebrile. The leukocytes were 14,200, with 60 per cent polymorphonuclears. The patient was discharged without operation, cured of the condition for which she had been admitted.

In 67 of the cases the retropharyngeal lymphadenitis advanced to the stage of suppuration. Of the 67 cases which suppurated, 4 ruptured spontaneously and a fifth was accidently ruptured during a digital examination. In 1 of the 4 which ruptured spontaneously the opening was subsequently enlarged to favor drainage. Although spontaneous evacuation is properly considered a dangerous accident because of the possibility of aspiration of pus into the air passages, we have never observed any bad results following spontaneous rupture. Of this subgroup of 5 cases, 4 were discharged cured and the fifth improved of the condition for which they were admitted to the hospital.

One of us recently had under our care a well-nourished girl, aged three years, with a large left-sided, rather low retropharyngeal abscess occurring as a complication of scarlet fever. As this occasioned no symptoms except difficulty in swallowing it was thought advisable to delay interference until there was more complete liquefaction. On examination late one evening it seemed to have reached the stage of maximum softening; the following morning it had completely subsided with entire relief of symptoms. The inference is that it ruptured spontaneously and the pus was swallowed.

Fifty-five of these 67 cases with suppuration were incised internally and 3 externally. Only once was it necessary to reincise because of inadequate drainage. Of these, 43 were discharged as cured and 14 improved; of the balance the data was incomplete, that is, 57 were relieved of the symptoms for which hospital admission was sought, 1 was removed against advice and 7 died. Of the cases which terminated fatally, 1 was cured of the retropharyngeal abscess but subsequently died of laryngeal diphtheria; another died of a complicating bronchopneumonia.

The following case is rather typical both in history and course of the average suppurative type which terminates favorably. This case, however, was not recognized by an experienced observer in the out-patient department, who attributed the respiratory difficulty to a pulmonary infection. Al. Pet., aged twenty-two months, showed a moderate degree of malnutrition, considerable inspiratory stridor with retraction of the episternal notch, pallor,

sweating and gutteral voice. The right cervical lymph glands were swollen; the tonsils were red and swollen and were pushed well forward. A retropharyngeal swelling the size of a walnut was observed at about the level of the tonsils on the right side. This was incised, and a large amount of pus obtained. A few hours following the operation the child was observed to have great difficulty in breathing. A direct smear from the abscess showed streptococci. The symptoms above mentioned rapidly subsided, and the child was discharged four days later cured of the condition for which he was admitted.

The following case illustrates the type most likely to escape recognition. Doubtless many such cases go on to recovery with incorrect diagnoses.

A. P., aged fourteen months, a well-developed and well-nourished infant, was brought to the out-patient department because of the swelling of the cervical region and slight fever. The swelling began on the left side and slowly subsided; subsequently the right side became involved, as noted on admission.

Slight interference with respiration was observed on admission; the tonsils were swollen, red and cryptic, and a small rather hard mass could be felt in the posterior pharyngeal wall. The retropharyngeal lymphadenitis gradually became more marked, and four days after admission it reached its maximum size. It then gradually subsided without interference, and twelve days after admission the child was discharged cured of his retropharyngeal lymphadenitis, but the left cervical lymph nodes were still slightly enlarged on discharge. Although no liquefaction was demonstrated, the blood examination showed 21,000 leukocytes with 81 per cent polymorphonuclears.

One infant died in the out-patient department directly following incision of the abscess, which was preceded by a digital examination of the pharynx by several of the staff. A child died in the hospital during a similar digital examination the day following incision of the abscess. It was reported to one of us that a child died recently in a Canadian hospital directly after repeated digital examinations.

Another case in our group was resuscitated with great difficulty following the same cause. The fatal results in the three cases enumerated, and the alarming symptoms in the fourth following so closely upon excessive digital examination, seem to decidedly emphasize its dangers.

Digital examination is necessary in some cases to determine whether lymphadenitis is present, and in others to determine whether fluctuation is present. Such examination should be conducted with the utmost speed and the minimum trauma. In many cases the swelling can be seen with the aid of a good light if the tongue is firmly depressed with a metal tongue depressor. From its size and appearance it can often be determined whether it has

suppurated. Digital examination is in our opinion contraindicated if the desired information can be obtained without it.

Whether the deaths in the cases under the above-mentioned circumstances were due to cardiac failure or cerebral congestion with hemorrhage or to other causes has not been determined by us. The death in one of the cases may probably be explained by the following: L. M., aged twenty-three months, was admitted to the Babies' Hospital, February 29, 1920. The chief complaint was "difficulty in breathing, increasing each day for ten days, and child had a cold two weeks ago." This was followed by a swelling of the right side of the neck; later marked respiratory difficulty was observed. The physical examination showed a well-nourished, well-developed boy, with considerable difficulty in breathing, inspiratory in type. A small swelling could be felt on the right side of the pharynx, behind the tonsils. The evening of the day of admission respiratory difficulty became more marked. At 11 P.M. the mass was opened with a hemostat, and about 1 dram of pus evacuated. Only slight relief was obtained. The following morning a mouth gag was introduced and the pharynx was examined with the finger. During the examination respiration ceased and efforts at resuscitation failed. Status lymphaticus was disclosed at autopsy. The findings were hyperplasia of spleen, lymph nodes, solitary follicles and Peyer's patches of the intestines.

As evidence that retropharyngeal lympharyngeal lymphadenitis, whether suppurative or non-suppurative, can but rarely be tuberculous except when it is secondary to tuberculous caries of the vertebræ, the following figures relating to the Pirquet test are presented: In 38 cases in which a Pirquet test was done, only 5 showed a positive reaction. This gives a rate of 13 per cent, which is less than the general average of the sick children admitted to the hospital, which in a recent analysis of 3742 cases showed 15.3 per cent to be positive.[4] Some significance may be attached to the possibility of a tuberculous gland infection in an infant, aged eleven months, who showed an extremely well-marked Pirquet reaction. This child had pertussis two months prior to admission to the hospital. Although he was discharged cured of the retropharyngeal abscess, the history and Pirquet reaction was suggestive especially when it is recalled that occasionally the pharyngeal tonsil is tuberculous.[5]

It is difficult to obtain proper cultures in a struggling infant after it has been subjected to an operation without an anesthetic. In 21 cases, however, satisfactory cultures were made at the time the abscess was incised. In 15 streptococci were demonstrated, either alone or associated with other organisms—usually staphylococci, evidently a contamination from the mouth. In 5 of the 15 cases a non-hemolysing form of streptococcus was obtained in pure culture and in 3 the Streptococcus hemolyticus. All of these 8

cases recovered. In 3 cases staphylococci were the only organisms which grew. In 1 case there was a triple infection of staphylococci, pneumococci and influenza bacilli; in 2 others the pneumococcus and staphylococcus were combined.

At the Babies' Hospital retropharyngeal abscesses are opened internally by passing the instrument into the mouth directly back to the posterior pharyngeal wall unless the abscess burrows laterally, and fluctuation is present externally. One case in the above group which was incised internally had in addition an external incision over the fluctuating area. Three others had only an external incision. Two of these cases were discharged cured and the others improved. The usual procedure is to insert a moderately pointed artery clamp into the abscess and withdraw it with the blades open. The finger is used as a guide to locate fluctuation, and to direct the artery clamp to the softest point. The mouth is held open with a tongue depressor in infants, and with a mouth gag in older children.

Summary. In a group of 72 cases of retropharyngeal lymphadenitis in infants and young children on which the end-results are known, including those which subsided spontaneously, those which broke down and ruptured spontaneously, and those which were incised, the mortality was 9.7 per cent. If the 7 non-suppurating cases are excluded the mortality rate was 10.7 per cent, which approximates the mortality rates reported by others.

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STUDIES IN GASTRIC ANALYSIS (DOUBLE SIMULTANEOUS FRACTIONAL ANALYSIS).

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It seems almost presumptuous to attempt to add anything to the already large literature on the use of the fractional method of gastric analysis. However, the appearance in that literature during the past few years of papers by Gorham,[1] Wheelon,[2] Kopeloff,[3] White[4] and Friedenwald *et al.*,[5] criticising the method through a

misconception of its fundamental assumptions and the physiological facts underlying these seemed to warrant the following contribution.

To review briefly these papers: Gorham says "The quantitative determination of the variation of gastric acidity during the different phases of digestion by the so-called 'fractional method of gastric analysis' is presumably based on the assumption that the gastric chyme after a test-meal is a homogeneous mixture and that a small portion, aspirated at fifteen-minute intervals, represents the acid concentration of the gastric contents as a whole at that period of digestion." He then showed by rapidly extracting 10-cc amounts forty-five minutes after a test-meal that there was marked variation in the acid values of the different samples, and concludes that "The true fractional analysis necessitates the giving of successive test-meals and extracting them at different periods."

Wheelon also states that fractional gastric analysis is based on the assumption that the gastric contents is a homogeneous mixture. He then proves that this is not so by a study of the acidity of samples obtained by the method of rapid divided extractions at one hour. He concludes that "A correct analysis of gastric activity can only be made when it is known (1) from what portion of the stomach the tube is delivering, (2) whether or not duodenal regurgitation is occurring, (3) the degree of motility of the stomach, (4) the secretory power of the stomach, (5) the effects of withdrawal on the motility and secretory function."

Kopeloff has done the most interesting work. He first studied the acidity of samples obtained by the method of rapid divided extractions, and found that there was considerable variation even in normal individuals. He states "The fraction obtained at any one moment cannot, therefore, be accepted as representative of the total gastric contents, for it is entirely dependent on the position of the tip of the tube in the stomach at the moment of withdrawal. Obviously, this position is necessarily a constantly changing one, due: (1) To the change of size and position of the stomach while emptying itself through the pylorus and by aspiration; (2) the shortening and lengthening of the stomach from gastric contraction; (3) the peristaltic waves that tend to carry the tube toward the pylorus." He then introduced three tubes into the same subject—one to a distance of 50 cm., one to a distance of 45 cm. and the other to 40 cm. Extractions were made simultaneously from each tube and fractional curves plotted. This was done on 3 patients. In discussing the results he says: "The fraction taken from the tube inserted to 40 cm. is almost invariably lower in total and free acidity than the fractions taken at a depth of 45 or 50 cm. Furthermore, these samples were totally different in physical character, being of a lighter color, often water-white,

and containing lesser amounts of starch. . . . Very little difference was found between fractions obtained at 45 and 50 cm., respectively. However, the fact that these two fractions are usually in close agreement indicates that in that region the stomach contents were, perhaps, of a more homogeneous character. In plotting the curves of fractions taken at each level, a certain general similarity may be noted, despite the recrossing at numerous points. This might seem to indicate that if the level of the tube were kept constant, single determinations might yield a characteristic curve. However, the errors are too fundamental to be thus lightly disregarded." In conclusion he states: "Aliquot fractions obtained by the Rehfuss method of gastric analysis cannot be assumed to represent accurately the total gastric contents."

White states: "Fractional analysis is based, either consciously or unconsciously, on the assumption that small fractions of the gastric contents represent the whole content of the stomach at the time, and that fractional curves, as ordinarily obtained, represent changes in gastric secretion." He then studied 50 cases by the method of rapid divided extractions, and demonstrated a marked variation in the acidity of the different samples. He summarizes in part as follows: "Fractional analysis is only a rough method of testing gastric secretion. Accidental variation may amount to 50 or 100 per cent of the figures obtained. Only gross changes in acid have clinical importance. The recognition of these limitations seems likely to lessen its use in the future."

Friedenwald agrees that the gastric contents is not a homogeneous mixture, and concludes that: "(1) Stomach contents are not homogeneous as evidenced by variations in fractions aspirated in rapid succession and by changing the position of the tip; (2) the tip resting in the pars media and pylorica gives fairly accurate information regarding gastric digestion; (3) variations may be reduced by mixing the contents of the stomach; (4) daily variations in acidity of gastric contents occurs, but this variation is moderate —a hyperacid, normal or hypoacid secretion continues as a rule to present the same character of acidity."

It is apparent from the above that all these authors are in general agreement as to the following points: They accept the statement of Gorham that "The fractional method of gastric analysis is presumably based on the assumption that the gastric chyme after a test-meal is a homogeneous mixture." They are all able to prove that the gastric contents is not a homogeneous mixture, therefore they either question the value or frankly condemn the fractional method of gastric analysis. Kopeloff came closest to the real purpose of fractional gastric analysis when he showed that curves obtained simultaneously from different parts of the stomach had the same general character, but that the physical characteristics of the material withdrawn showed marked differ-

ences. However, he seems to have disregarded these findings in his conclusions and to be in agreement with the other authors cited.

These criticisms, I firmly believe, are not justified, and tend to shake the confidence of the profession at large in a clinical procedure of great value in the proper study of the gastro-intestinal tract. In the first place, after a careful review of the literature I can find no statement by any advocate of the fractional method, that the samples extracted are representative of the whole stomach contents, and therefore it seems to me that the "presumption of the assumption" on the part of Gorham is unwarranted. In the second place, any variation in the acid values of different parts of the stomach is based on the physiology of the organ, and the proof of such variation cannot be used as argument against a method admitting such variation. A short recapitulation of the fundamental principles, purposes and limitations of fractional analysis and a review of the anatomy and physiology of the stomach may not be out of place and will serve as a foundation for the subsequent development of the subject.

As I have just said, fractional analysis is not based on the assumption that the samples extracted are representative of the whole stomach contents at that time. It is not primarily interested with the stomach contents as a whole at any one time but rather in studying, by sample extractions from the proper point, the result of the action of the stomach on the food material introduced. As has been repeatedly emphasized, especially by Rehfuss and Hawk,[6] fractional analysis is a measure of gastric work, and for the sake of convenience the sum total of gastric work may be divided into different periods and factors. The first period is the interdigestive phase, represented by the fasting stomach. As the stomach is never entirely idle this represents the base line of secretory and motor activity, and it also affords the opportunity to study any additions to the stomach contents from above or below since these additions are then present in their greatest concentration and are not obscured by the material undergoing digestion. During the second period, the digestive phase, the gastric work may be considered in three general divisions: The first of these, and relatively the least important, is the secretory response as determined by the amount of gastric juice added to the digestion mixture; the second is the amount of comminution of the material serving as the test load and its mixture with the gastric juice; the third factor is the rapidity with which the stomach passes on the test load or, in other words, the motor end point. While all these factors are interrelated to a certain extent, still anyone of them may vary independently of the others, and it is only by studying all of them that a true estimate can be obtained of the response of the stomach to the test load. As was previously pointed out,[7] fractional analysis is not a simple procedure, and any technic that

does not take into consideration all of the above factors does not return the greatest possible amount of information. As fractional analysis is only to be considered as a measure of gastric work expressed in the three factors of secretory response, mechanical division and mixing and motor end point, only those pathological processes which alter one or more of these factors are susceptible of demonstration by this method. We cannot hope to demonstrate changes in form, position, contour or mobility.

The findings of the anatomist and physiologist regarding the stomach that have a direct bearing on the question of fractional gastric analysis are as follows: Embryologically the stomach is a straight tube surrounded by circular bundles of muscle fibers, and it is by bending and a ballooning-out of one side of this tube that the adult form of the stomach is gradually produced. During fetal development there is a quite distinct division of the stomach into different parts suggesting the condition found in the compound stomach of ruminants.[8] The fixed points of the stomach are the cardiac and pyloric ends, and, whereas the distance between these points along the lesser curvature maintains a definite relation to the size of the growing individual, the increased capacity of the stomach is obtained by a distention of the greater curvature. In the arrangement of the oblique muscle fibers there is a mechanism for reducing the size of the fundus, for the lines of force exerted by the contraction of these bundles, aided by the circular fibers, would tend to restore the organ to its original tubular form.

There is also a difference in the histology of the mucosa of the different ends of the stomach, and Radasch[9] has shown that the transition from one to the other is quite sharp, especially as regards the acid cells. This anatomical arrangement would suggest that even in the adult human stomach there is a division into two definite parts, and this conclusion is further supported by a consideration of the physiology of the cardiac and pyloric ends of the organ. Alvarez[10] has demonstrated graded differences in rhythmicity, irritability, tone and latent period between the muscle of different parts of the stomach. Roentgen-ray observers have noted that during the height of digestion peristaltic waves may be seen originating high in the fundic portion and progressing as shallow indentations, pass over the organ until a point is reached, at a fairly definite distance from the pylorus, where each wave changes its character, deeply identing the outline of the stomach and at times completely obliterating the lumen. It has long been known that the acid of the gastric juice was formed in the fundus, and Ivy and Oyama[11] have recently shown that the secretion of the pyloric part is definitely alkaline. Thus anatomy and physiology both point to the fact that the stomach cannot be considered as a whole but rather as an organ with two distinct parts differing in form, structure and function. The fundus serves as a reservoir or hopper for

the rapid reception of large amounts of food. Here salivary digestion continues in the interior of the mass while the outer layer, composed of the food first ingested, is subject to the action of the gastric juice. Aided by the gentle pressure exerted by the fundus, which pressure nicely adjusts itself to the amount of food present, the softened outer layers of the mass are gently stroked toward the pyloris. Here the semifluid material is kneaded by the vigorous peristaltic waves passing over the antrum until the individual masses have become finely comminuted and the whole intimately mixed with the gastric juice. At this point the pylorus opens and the chyme is ejected into the duodenum. Alvarez says "It is now well known that there are three parts of the stomach: (1) The fundus, which holds the food fairly motionless, often in layers, as it comes in; (2) the muscular antrum, which breaks the food up and mixes it with the gastric juice; (3) the canalis gastricus, which carries fluid along the lesser curvature and out into the duodenum."

With this conception of fractional analysis and the physiology of the stomach, the present investigation was undertaken, the object being to demonstrate if possible the following points:

1. That, although differing in acid values, if a constant relation be maintained between the points of extraction, fractional curves from different parts of the stomach would not cross but be similar.
2. To show the difference in the physical properties of samples from different parts of the stomach.
3. To show that extractions from the antrum give the most information as to the work being done by the stomach.

Technic. The apparatus used was modified from that of Epstein[12] and consisted of two standard duodenal tubes with Lyon tips. One tip was grooved along its lateral surface, so as to receive the tube passing to the more distal tip. In order that the two tips should maintain a definite relation to each other, the grooved tip and tube were lashed to the other tube in such a position that the tips were 10 cm. apart.

The patients presented themselves six hours after a test-breakfast and the double tube was passed. No serious difficulty was encountered, although in most instances this represented the patient's first experience with gastric intubation. The amount of the tube to be introduced in each case was roughly estimated by placing the upper or grooved tip at the xyphoid and measuring on the tube the distance to the patient's upraised chin. Introducing the double tube to this distance was found to bring the lower tip well into the antrum, with the upper tip in the fundus along the lesser curvature. With this arrangement the tips maintained a constant relationship to each other, and varied as little as possible their relative position in the stomach, as it was shown that the lesser curvature was the least subject to change in length and position during the process of digestion.

With the tube in position, as much of the fasting content as possible was extracted through the upper tip, and the stomach was then completely emptied through the lower tip. In this way not only the differences in acidity but also the differences in physical properties and amount of material in the two parts could be noted. The standard Ewald meal was then eaten with the tubes *in situ*. Extractions were made at half-hour intervals simultaneously from both tubes, and the notes and titrations recorded at once. Great care was taken to free the tube of its contents after each extraction by injecting air, but this was done with caution so that the tube was just emptied and little or no air escaped from the tip, for if any large amount were injected it would tend to disturb the digestion mixture as it ascended into the fundus. At the two-hour period as much material as possible was extracted through the upper tip and immediately following this the stomach was completely emptied through the lower tip. A test-lavage was then given with plain water, which was run in through the upper tip and siphoned off through the lower tip. In this way it was made certain that the stomach was entirely empty. During the entire procedure the patients were instructed to expectorate all saliva into a receptacle.

Discussion. The charts presented herewith are representative of the results of double gastric analysis as outlined above. The patients were all attending a gastrointestinal clinic and, therefore, none of the series can be taken as normal. However, as no attempt was being made to fix the normal, more information was to be expected from patients with gastrointestinal complaints.

In regard to the information obtained bearing on the original points of investigation, I think that the demonstration is conclusive. The first object of this investigation was an endeavor to show that fractional curves from different parts of the stomach would be similar. Chart I is typical of the results obtained when the curves were uninfluenced by biliary regurgitation. It will be seen that the acidity of extractions from the fundus and the antrum form entirely similar curves differing only in acid value. This similarity was also demonstrated in cases of achylia and hyperacidity, but space does not permit the presentation of these charts. A point of interest is that, although the hydrochloric acid is secreted in the fundus the highest acid values were found in the antrum. I believe that the answer to this point lies in a difference in concentration, or rather dilution, of the acid as secreted, but further work will have to be done on the point. It will also be noticed that, with the bread and water meal, there is a tendency for the contents of the two parts of the stomach to have the same acid values during the second hour, except in those cases in which the acidity continues to mount during the second hour. This finding is probably due to the diffusion of the acid through the rather fluid

meal, and in the usual mixed meal of the normal diet would not occur to such a marked degree.

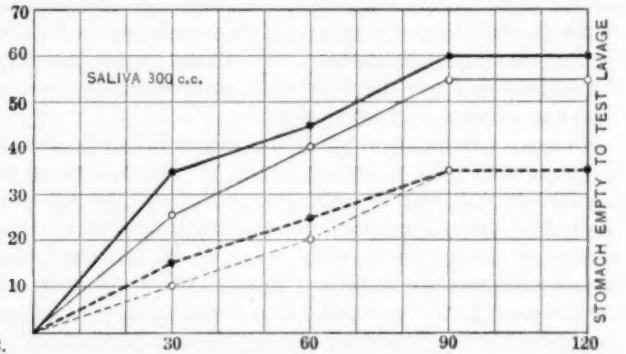
As is noted on Chart I, *B* and *C* on the line marked chyme stand for bread and chyme. In those marked *B* the extraction contained small crumbs of bread in water and on straining through gauze or cotton the filtrate is water-clear. In those marked *C* the material extracted is thicker, homogeneous or finely granular, creamy in color and even on straining the filtrate is a little turbid. It must be assumed that this change in the character of the extractions is due to the peristaltic activity of the antrum, and represents the comminution of the test-substance and its mixing with the gastric juice. This is part of the work of digestion done by the stomach, and the performance of this work can be followed through the fractional gastric analysis. In all the charts it will be seen that the extraction from the fundus contained bread crumbs, and that from the antrum contained chyme.

From an examination of all the charts it can be seen that, except in those with biliary regurgitation, all the factors of gastric work can best be followed by extractions through the tip in the antrum. Even in those cases with biliary regurgitation, although a true picture of the gastric acidity may not be obtained, the important fact of the presence of biliary regurgitation would be missed unless the tip were in the antrum. The ideal place to study gastric work would be the first part of the duodenum, providing regurgitation from beyond could be effectually blocked. As this is not routinely practical we must be content with the extractions through the tip in the antrum.

This work is in entire accord with that of Lockwood and Jacobson,[13] who say "Obviously the acidity of any one portion extracted through the small tube depends on the location of the tip of the tube and gives the character of the contents of that part at the time. Just as obvious is the assumption that if the tube stays in the same place one could, by extracting at definite intervals, obtain the cycle of events through a long period. This we believe is what happens and the reason one gets such beautiful curves in the majority of cases. Any marked sudden deviation of the curve can be explained by a change in the position of the tip, or by duodenal regurgitation. The chief cycle of stomach chemistry takes place in the pars media and pars pylorica which are the lowest parts of the organ. If the tube is of sufficient weight to sink in the stomach contents, and if the patient remains in the sitting position or if reclining remains supine, these conditions are in the majority of cases fulfilled and a steady curve is obtained. Repeated roentgen-ray observations have convinced us that the tube tip, due to gravity and peristalsis, generally rests near the outlet of the stomach, therefore the fractional method with proper technic represents the cycle at that most important portion of the stomach,

allowing one to observe the acidity, presence of pathological products, duodenal regurgitation and the presence or absence of food."

On examining these charts there are several other points besides those already mentioned that are of considerable interest. Chief among these is the question of biliary regurgitation. Entirely aside from whether biliary regurgitation is normal or not, these charts present the subject from a somewhat different angle. All the charts presented, with the exception of Chart I show biliary regurgitation in one or more of the fractional extractions, and the most striking thing about the regurgitation is that it appears only in the extractions from the antrum. In no instance was bile



	F.C.		30		60		90		120	
FREE	0	0	10	15	20	25	35	35	35	35
TOTAL	0	0	25	35	40	45	55	60	55	60
CHYME			B	C	B	C	B	C	B	C
MUCUS			2	0	0	0	0	0	0	0
BILE			0	0	0	0	0	0	0	0
Oc.Bl.			0	0	0	0	0	0	4	1
AMOUNT	0	0	8	5	6	5	5	4	23	105

CHART I.—In this and subsequent charts solid lines denote total acidity and broken lines free hydrochloric acid. Heavy lines are extractions from the fundus; light lines are from the antrum. Notes in left hand column refer to fundus; those on right to extractions from the antrum. Scale 0, 1, 2, 3, 4, Amounts in cc. Note similarity of curves.

present on inspection in any of the samples taken from the fundus, although it was present at the same moment in the antrum in concentrations ranging from a faint yellow tinge to a deep yellow. The most generally accepted theory as to the purpose of biliary regurgitation is that it is a mechanism of the intestinal tract to overcome the supposedly high acid values existing at that time in the stomach. From an analysis of these charts that theory seems hardly acceptable since it is shown that the regurgitated bile never reaches the fundus of the stomach where, during most of the digestion period, the large mass of food is held. But of even greater interest than the fact that the entire stomach contents is not affected by the regurgitation of bile is the fact that, while

there is biliary regurgitation into the antrum with a consequent lowering of the acidity, the acidity of the fundus may continue to rise and even reach considerable heights (Charts III and IV). That biliary regurgitation is not necessarily associated with high acid concentration is shown in Chart II, where the acidity of the fundus is only 20 free and 40 total, and yet there is biliary regurgitation Scale 3. Up to the present the very fact of the finding of biliary regurgitation presupposed a hyperacidity, for, no matter what the acidity of the sample containing the bile, it was presumed to have been cut to that point from an abnormally high acidity. The taking of simultaneous extractions from the fundus has shown that biliary regurgitation occurs in cases with low original acidity. Another phase of biliary regurgitation that these charts throw some

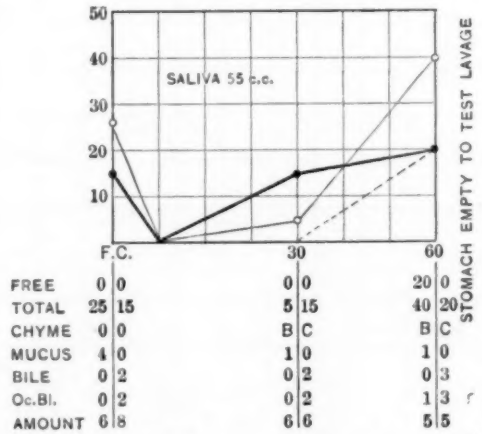
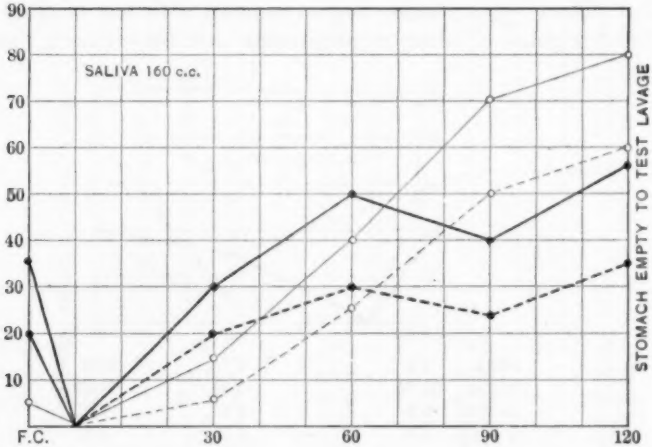


CHART II.—Crossing of curves for total acidity is due to biliary regurgitation into the antrum. This was sufficient to entirely neutralize the free hydrochloric acid in the specimen at sixty minutes.

light on is the question of exactly how much biliary regurgitation is capable of cutting the acidity of the gastric juice. Charts II and IV of this series throw most light on this question. In Chart II it will be seen that a Scale 3 regurgitation at sixty minutes' cut the acidity of the antrum to 0 free and 20 total, while the simultaneous extraction from the fundus showed values of 20 free and 40 total. This is a cut of at least 50 per cent in the total acid and a complete neutralization of the free acidity. In Chart IV a Scale 4 regurgitation at one hundred and twenty minutes caused a cut from 85 free and 110 total in the fundus to 25 free and 55 total in the antrum. This is a really surprising reduction and yet represents a cut of only 50 per cent in the total acidity.

These findings strengthen the conclusion that biliary regurgitation is not primarily caused by high acid concentrations in the

stomach. If we cannot find the cause of reverse peristalsis in changes in the contents of the digestive tract then we must look for the cause in the changes in the muscular wall of the tube. The normal direction of flow of the contents is aboral, and Alvarez has explained the mechanism of this in the gradient idea. Reversal of flow has been repeatedly demonstrated, and in several locations has even been considered physiological by certain investigators. It has also been demonstrated that any irritative lesion affecting the musculature of the digestive tube increases the degree and frequency of reverse peristalsis, especially in portions of the diges-



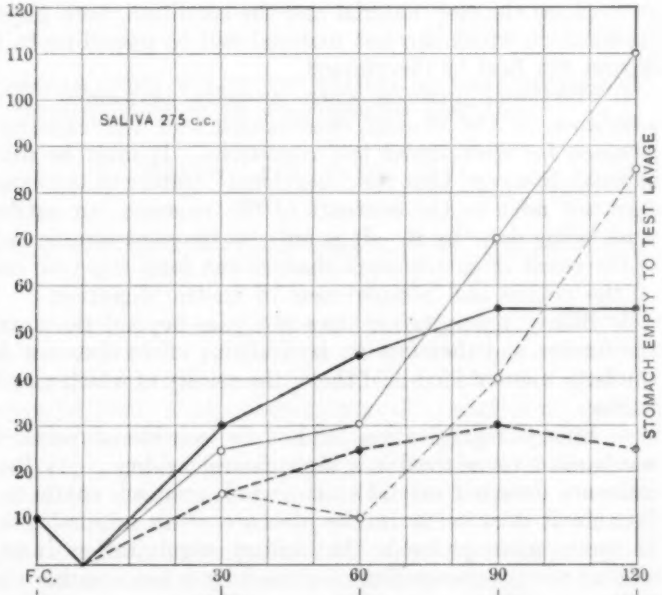
	F.C.		30		60		90		120	
FREE	0	20	5	20	25	30	50	25	60	35
TOTAL	5	35	15	30	40	50	70	40	80	55
CHYME	0	0	B	C	B	C	B	C	B	C
MUCUS	4	0	1	0	1	0	1	0	1	0
BILE	0	0	0	0	0	0	0	2	0	2
Oc.Bl.	0	1	1	1	0	0	1	3	1	1
AMOUNT	5	60	5	7	3	5	3	4	8	3

CHART III.—Crossing of curves for both total acidity and free hydrochloric acid due to biliary regurgitation. Acidity in fundus continues to ascend.

tive tube above the lesion. It seems more plausible then to assume that biliary regurgitation, especially during digestion when the flow of contents in the canal should be most definitely and continuously aboral, is to be considered as evidence of an irritative lesion disturbing the normal gradient, the lesion in all probability being distal to the pylorus.

Another point that is brought out by these charts is that the tip of the tube must remain in the same position throughout the test if the information obtained is to be accurate. If during the course of a fractional analysis the tube should slip in or out, it must be returned to its original level before the next extraction is made.

Likewise if there is any difficulty in making any of the extractions it is not permissible to pull the tip out a little way or to inject air in any quantity to free the tip. These procedures will either change the position of the tip in the stomach or so disturb the digestion mixture that the acid value of the sample so obtained will not represent a direct continuation of the curve built up from the previous extractions.



FREE	0		15	15		10	25		40	30		85	25
TOTAL	10		25	30		30	45		70	55		110	55
CHYME	0		B	C		B	C		B	C		B	C
MUCUS	4		0	0		0	0		4	0		4	0
BILE	0		0	0		0	0		0	1		0	4
Oc.Bl.	0		0	0		0	0		4	1		4	1
AMOUNT	0	15		8	6		4	6		3	6		16	45

CHART IV.—Crossing of curves due to biliary regurgitation. At one hundred and twenty minutes this is sufficient to cut the acidity of the fundus in half.

Summary. 1. Simultaneous fractional gastric analysis from two points in the stomach definitely fixed 10 cm. apart produce curves that are entirely similar in their general characteristics except where influenced by biliary regurgitation. The acid values from the antrum are always higher than those from the fundus except where the former are cut by biliary regurgitation. With the bread and water meal there is a tendency for the acid values of the two parts to become equal during the second hour due to the diffusion of the acid through the fluid meal.

2. There is a recognizable difference in the physical properties of the extractions from the fundus and the antrum, this change being due to the comminution of the test substance by the peristaltic activity of the antrum. If this comminution is not found in extractions from the antrum it is evidence that the stomach is not doing a portion of the work it normally should do.

3. The antrum, close to the pylorus, is the best place to study gastric function for there the stomach has most nearly completed its work on the test material and the condition, both physical and chemical, in which the test material will be passed on to the duodenum can best be determined.

4. Fractional analysis when properly performed is of great assistance in the clinical determination of the capacity of the stomach for work under test conditions. It must be firmly kept in mind, however, that the "fractional" feature of the examination does not refer to the contents of the stomach but rather to the work being done by it. It is only by frequent sample extractions of the result of gastric work that we can form any true conception of the course and completeness of gastric digestion.

5. Biliary regurgitation does not pass beyond the antrum into the fundus and therefore its neutralizing effect does not extend to the large mass of food held there, the acidity of which may continue to rise.

6. Biliary regurgitation cannot be considered primarily as a mechanism to neutralize a high gastric acidity: (1) Because its influence does not extend to the whole stomach contents, and (2) because it does occur in the presence of an original low acidity. It seems more probable that biliary regurgitation is an expression of the reverse peristalsis caused by a lesion either directly or indirectly irritating the muscular wall of the intestinal tract.

7. Any change in the position of the tip of the tube during the course of the test alters the curve and defeats the object of the fractional type of analysis.

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THE COMPARATIVE VALUE OF BLOOD TRANSFUSION AND BLOOD TONICS IN SECONDARY ANEMIAS.*

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There are several reasons for the widespread use of blood transfusion of recent years: (1) The just recognition of the procedure as an effective therapeutic measure. (2) The observation made by Landsteiner, in 1900, of the phenomenon of iso-agglutination and the practical elaboration of that phenomenon by Jansky and later Moss; the proper grouping and testing of the blood of the donor with that of the recipient has eliminated the alarming reactions following blood transfusion, which sometimes proved fatal. (3) The surmounting of the mechanical difficulties incidental to blood transfusion through the revival of the von Ziemssen syringe method in this country by Lindeman and the recent improvements in technic, one of which I have described,[1] in which the syringe is employed.

Phenomena of Red Cell Regeneration. The recent investigations of Drinker, Drinker and Lund[2] on the circulation of the blood in bone marrow, have shed some light on the phenomena which are instrumental for the appearance of the red cells in the blood stream. They have observed that the delivery of the red blood cells to the blood stream, in the absence of bone-marrow disintegration, is controlled by the growth pressure of the developing erythrocytes. The stimulus which is responsible for the proliferation of the red cells also causes the passage of these cells through the delicate walls of the marrow capillaries. The relative fall in pressure level between the red cell forming areas and the adjacent capillaries on the one hand and the areas of developing erythrocytes and

* Read before the Eastern Medical Society of the City of New York, March 14, 1924.

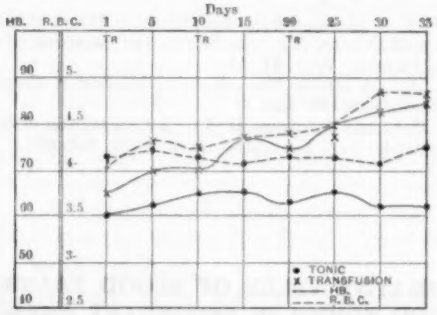

FIG. 1.—Graphic chart showing comparative results with blood tonic and blood transfusion. Patient F. R. F. Furunculosis. Fowler's solution M. 5. Tr.—Transfusion days.

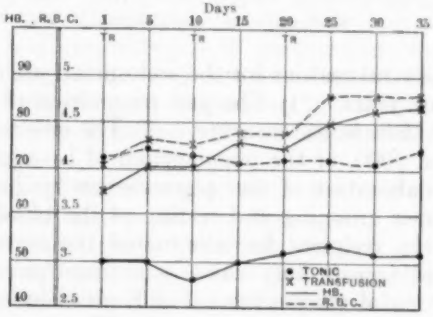

FIG. 2.—Patient J. J. R. Chronic gonorrheal arthritis. Caccodylate of iron.

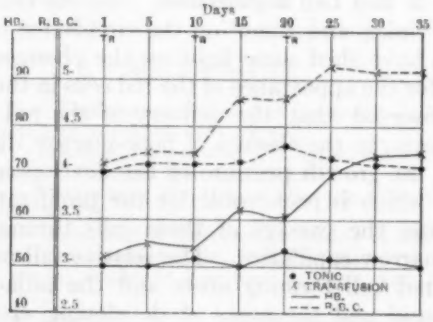

FIG. 3.—Patient J. McG. Chronic osteomyelitis tibia. Blaud's pills.

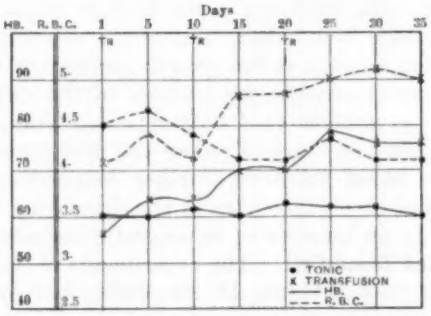

FIG. 4.—Patient H. H. Chronic nephritis. Basham's mixture.

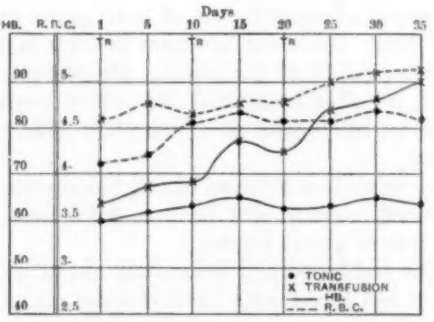

FIG. 5.—Patient R. F. Convalescing lobar pneumonia. Ferrous iodide.

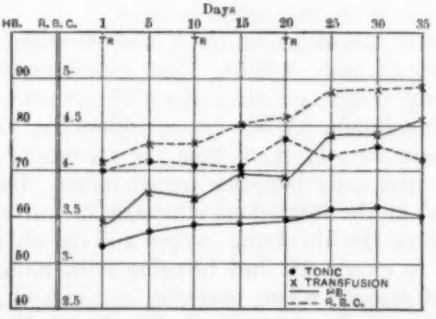

FIG. 6.—Graphic chart showing comparative average results obtained from administration of inorganic iron and arsenic preparations and blood transfusion in the 10 cases studied.

surrounding marrow on the other is the determining factor for the delivery of red cells following bone marrow stimulation. Thus, after a single large hemorrhage immature red corpuscles appear in the circulation as soon as the growth pressure of the stimulated erythropoietic areas exceeds the pressure of the surrounding bone marrow, but it is possible that after repeated hemorrhage a stage of adjustment may be reached where the immature forms do not appear in the blood following further hemorrhage. Therefore, absence of immature erythrocytes in the circulating blood does not mean necessarily an inactive or hypoplastic marrow.

Life of the Red Blood Cell. The experiments of Ashby,[3] based on the transfusing cells of Group IV into individuals of unlike group and observing the time that elapses until the disappearance of the transfused cells, have shown that the length of life of a transfused corpuscle in a normal individual is about thirty-nine days.

The Role of Iron in Animal Life. Iron has long been recognized as one of the essential constituents of both plant and animal life. In the animal body the chief function of iron is to supply and maintain the hemoglobin of the blood. Hemoglobin is an organic iron compound, peculiar to animal life, which possesses a special chemical property by means of which it is able to absorb and condense oxygen.

The twenty-five million millions of red blood cells floating in the blood of a man of average size have a combined area of about 22,000 square feet or about ½ acre.

The life of the red blood cell being only about six weeks, of the total number of red blood cells 7,000,000 die every second of our lives, and in order to keep the number normal and constant an equal number must be created by the blood-forming organs of the body every second, which is a striking example of the remarkably intense activity of those organs and of their essential importance for the maintenance of the normal balance.

The body of a man weighing 150 pounds contains 1 part of iron to 24,000 parts of body weight. The blood, constituting 7 per cent of the body weight, contains about 95 per cent of the iron, in the form of hemoglobin. When one considers that the entire body normally contains but 44 gr. of iron, the wisdom of administering 5 to 15 gr. of iron daily becomes questionable. One cannot help but be amazed at the marvelous efficiency of but a few grains of iron in entrapping the life-giving oxygen and circulating it throughout the body to every cell and bringing it in immediate contact with the most minute waste particles, and carrying back to the lungs the products of combustion in the form of carbon dioxide, by far the most bulky and most important of our excretions, amounting to more than forty times the weight of urea eliminated and 400 times the weight of uric acid excreted.

TABLE I.—TONIC ADMINISTRATION.

Patient.	Age.	Sex.	Cause of anemia.	Drug.	Hb.—Days.								R.B.C.—Days.							
					1	5	10	15	20	25	30	35	1	5	10	15	20	25	30	35
F. R. F.	26	M.	Furunculosis	Fowler's	60	63	65	65	63	65	62	62	4.1	4.3	4.2	4.1	4.2	4.2	4.1	4.3
J. J. R.	21	M.	Chronic gonorrheal arthritis	Caccodylate of iron	50	50	46	50	52	54	52	52	3.8	3.6	3.6	3.8	3.8	4—	4.1	4—
H. L. F.	30	M.	Asthenia	Caccodylate of iron	46	50	54	60	66	70	78	74	3.4	3.6	3.9	4.2	4.6	4.6	4.8	4.6
J. L.	42	M.	Chronic rheumatic arthritis	Blaud's pills	54	56	54	50	52	56	56	54	3.8	3.8	3.6	3.6	3.8	4—	4—	4.1
L. R.	38	F.	Sciatica	Ferrous iodide	68	68	70	66	70	72	74	70	4.1	4.2	4.2	4—	4.2	4.4	4.5	4.4
J. McG.	44	M.	Chronic osteomyelitis	Blaud's pills	50	50	52	50	54	52	52	50	4—	4.1	4.1	4.2	4.4	4.2	4.2	4.1
H. H.	36	M.	Chronic nephritis	Basham's mixture	60	60	62	60	64	62	62	60	4.5	4.7	4.4	4.2	4.2	4.4	4.2	4.2
L. V. S.	32	M.	Chronic bronchitis	Citrate of iron	56	58	58	60	62	64	68	66	4—	4.2	4.3	4.4	4.2	4.1	4.2	4.3
R. F.	24	F.	Convalescing lobar pneumonia	Ferrous iodide	60	62	64	66	64	66	66	64	4.2	4.4	4.6	4.8	4.6	4.6	4.8	4.6
S. F.	46	F.	Chronic nephritis	Basham's mixture	52	52	54	52	50	52	50	50	4.1	4.2	4.1	4.3	4.1	4.2	4.2	4.1

TABLE II.—BLOOD TRANSFUSIONS AT TEN-DAY INTERVALS.

Patient.	Age.	Sex.	Cause of anemia.	Treatment*	Hb.—Days.								R. B. C.—Days.							
					Tr. 1	5	Tr. 10	15	Tr. 20	25	30	35	1	5	10	15	20	25	30	35
F. R. F.	26	M.	Furunculosis	.....	65	70	70	78	74	80	82	83	4.1	4.3	4.2	4.4	4.4	4.8	4.8	4.7
J. J. R.	21	M.	Gonorrheal arthritis	.....	54	58	58	64	64	72	70	70	4—	4.4	4.2	4.6	4.4	4.8	4.6	4.6
H. L. F.	30	M.	Asthenia	.....	66	74	72	78	76	86	94	92	4.6	4.8	4.8	4.6	5—	5.2	5.2	5.2
J. L.	42	M.	Chronic rheumatic arthritis	.....	54	58	64	62	64	70	68	76	3.8	4—	3.8	4.2	4.2	4.6	4.4	4.4
L. R.	38	F.	Sciatica	.....	70	78	76	84	84	88	90	92	3.8	4.2	4.2	4.6	4.8	5.2	5.1	5.1
J. McG.	44	M.	Chronic osteomyelitis	.....	52	56	54	62	60	70	72	74	4.2	4.4	4.4	4.8	4.8	5.2	5.2	5.1
H. H.	36	M.	Chronic nephritis	.....	58	64	62	70	70	78	76	76	4.1	4.4	4.2	4.8	4.8	5—	5.1	5—
L. V. S.	32	M.	Chronic bronchitis	.....	62	66	62	70	68	76	76	82	4—	4.2	4.2	4.6	4.8	4.8	5—	5.1
R. F.	24	F.	Convalescing lobar pneumonia	.....	64	68	68	78	76	84	86	90	4.6	4.8	4.6	4.8	4.8	5—	5.1	5.2
S. F.	46	F.	Chronic nephritis	.....	50	54	50	58	56	66	70	74	4—	4.1	4.2	4.4	4.2	4.6	4.6	4.8

* Blood transfusion at ten-day intervals.

Tr. Transfusion days.

TABLE III.—COMPARATIVE RESULTS WITH BLOOD TONICS AND BLOOD TRANSFUSIONS.

Patient.	Age.	Sex.	Cause of anemia.	Treatment.	Hb.—Days.														R. B. C.—Days.											
					1		5		10		15		20		25		30		35		1		5		10		15		20		25		30		35	
					To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr	To	Tr
F. R. F.	26	M.	Furunculosis	Fowler's	60	65	63	70	65	70	65	78	63	74	65	80	62	82	64	83	4.1	4.1	4.3	4.3	4.2	4.2	4.1	4.4	4.2	4.4	4.2	4.8	4.1	4.8	4.3	4.7
J. J. R.	21	M.	Chronic gonorrheal arthritis	Cacodylate of iron	50	54	50	58	46	58	50	64	52	64	54	72	52	70	52	70	3.8	4—	3.6	4.4	3.6	4.2	3.8	4.6	3.8	4.4	4—	4.8	4.1	4.6	4—	4.6
H. L. F.	30	M.	Asthenia	Cacodylate of iron	46	66	50	74	54	72	60	78	66	76	70	86	78	94	74	92	3.4	4.6	3.6	4.8	3.9	4.8	4.2	4.6	4.6	5—	4.6	5.2	4.8	5.2	4.6	5.2
J. L.	42	M.	Chronic rheumatic arthritis	Blaud's pills	54	54	56	58	54	64	50	62	52	64	56	70	56	68	54	76	3.8	3.8	3.8	4—	3.6	3.8	3.6	4.2	3.8	4.2	4—	4.6	4—	4.4	4.1	4.4
L. R.	38	F.	Sciatica	Ferrous iodide	68	70	68	78	70	76	66	84	70	84	72	88	74	90	70	92	4.1	3.8	4.2	4.2	4.2	4.2	4—	4.6	4.2	4.8	4.4	5.2	4.5	5.1	4.4	5.1
J. McG.	44	M.	Chronic osteomyelitis	Blaud's pills	50	52	50	56	52	54	50	62	54	60	52	70	52	72	50	74	4—	4.2	4.1	4.4	4.1	4.4	4.2	4.8	4.4	4.8	4.2	5.2	4.2	5.2	4.1	5.1
H. H.	36	M.	Chronic nephritis	Basham's mixture	60	58	60	64	62	62	60	70	64	70	62	78	62	76	60	76	4.5	4.1	4.7	4.4	4.4	4.2	4.2	4.8	4.2	4.8	4.4	5—	4.2	5.1	4.2	5—
L. V. S.	32	M.	Chronic bronchitis	Citrate of iron	56	62	58	66	58	62	60	70	62	68	64	76	68	76	66	82	4—	4—	4.2	4.2	4.3	4.6	4.4	4.6	4.2	4.8	4.1	4.8	4.2	5—	4.3	5.1
R. F.	24	F.	Convalescing lobar pneumonia	Ferrous iodide	60	64	62	68	64	68	66	78	64	76	66	84	66	86	64	90	4.2	4.6	4.4	4.8	4.6	4.6	4.8	4.8	4.8	4.8	4.6	5—	4.8	5.1	4.6	5.2
S. F.	46	F.	Chronic nephritis	Basham's mixture	52	50	52	54	54	50	52	58	58	56	52	66	50	70	50	74	4.1	4—	4.2	4.1	4.1	4.2	4.3	4.4	4.1	4.2	4.2	4.6	4.2	4.6	4.1	4.8
				Averages	55.6	59.5	56.9	64.6	57.9	63.7	57.9	70.4	60.5	69.2	61.3	77.0	62.0	78.4	60.4	80.9	4.0	4.1	4.1	4.3	4.1	4.3	4.1	4.5	4.4	4.6	4.2	4.9	4.3	4.9	4.2	4.9

Tr., Transfusions. To., Tonics.

The Negative Effect of Iron and Arsenic on Blood Regeneration. Since Menghis, in 1746, reported that he had found iron in the blood of man, the value of inorganic iron as a therapeutic agent has been both confirmed and denied by various medical men. With the abandonment, in 1906, by Abderhalden, of his contention that inorganic iron could not be converted into hemoglobin, it has been generally accepted since as a valuable therapeutic agent in combating anemia. In 1920 Whipple[4] and his co-workers reopened the controversy by a series of publications of their studies of regeneration of the blood in anemia due to hemorrhage. In a series of papers they show that inorganic iron in the form of Blaud's pills and arsenic in the form of Fowler's solution has little or no effect on blood regeneration without proper diets, and they come to the conclusion that "We may not assume, without positive proof, that inorganic iron is of value in the treatment of simple anemia."

Object of Experiment. The present series of experiments were undertaken for the purpose of determining whether the conclusion of Whipple and his co-workers holds true in secondary anemias in general, rather than those which occur after a single, large, massive hemorrhage. Another object of this experiment was to make a comparison between the effects of inorganic iron and arsenic preparations administered for a period of thirty days and repeated blood transfusion, each of 500 cc, performed by the author's method, at ten-day intervals for an equal period of time.

Method of Experimentation. Ten patients in all were studied. They were young and middle-aged individuals of both sexes, who were suffering from anemia due to either acute or chronic illness.

The patients were each given a thorough physical examination, special pains being taken to search for any signs of damage or deficiency to the blood-forming organs, and a Wassermann and complement-fixation test of the blood were performed. Complete blood counts by the usual method and hemoglobin estimation was made by the Sahli method. Hemoglobin and red blood cell counts were done at five-day intervals during the course of the treatment and charts of the findings were kept.

Since diet plays a very important role in blood and hemoglobin regeneration, they were not placed upon any special diet, but were instructed to eat the same quality and quantity of food which they usually eat.

In order to obtain the coöperation and good faith of each patient the purpose of the experiment was explained to them, and the importance of the results, not only as regards themselves, but as directly concerning humanity was emphasized to them.

The following standard drugs were employed:

Fowler's solution, 5 minims, after each meal.

Cacodylate of iron, 1 gr., three times daily after meals.

Blaud's pills, each pill containing 3 gr. of carbonate of iron, 1 pill, three times daily, after meals.

Basham's mixture, 4 dr., well diluted, after meals.

Saccharated ferrous iodide, 5 gr., three times daily, after meals.

Ammonio-citrate of iron, 10 minims, three times daily, after meals.

Findings. The accompanying tabulations of findings resulting from the administration of either of the above drugs for a period of thirty days shows an average gain in hemoglobin of 5 per cent and a gain of 200,000 in the red blood cells—an increase which is so small as to be accounted for by the human shortcomings in determining the hemoglobin or calculating the red blood cells.

Blood transfusions caused an average increase in the hemoglobin of 21 per cent and 800,000 in red blood cells, with a decided and very apparent improvement in the general physical condition of the patients.

Discussion. The observations made in this group of patients confirms the findings of Whipple[4] and his co-workers and Musser,[5] that iron and arsenic preparations have a negative effect on blood regeneration and the correction of anemia. The individuals selected for this experiment were taken at random, and were subjected to a careful examination for any pathological condition or deficiency in their blood-forming organs. Of course, no two individuals are alike as regards their environment, hygienic conditions, habits, recuperative powers and reactions to food, all of which are important factors for hemoglobin and red blood cell regeneration. An effort was made, however, to maintain them as nearly as possible under the same conditions both under the drug and transfusion treatment.

Summary. 1. Individuals suffering from secondary anemia due to acute or chronic disease regenerate hemoglobin and red blood cells more rapidly, more effectively, more completely and within a shorter period of time by periodic blood transfusion than those receiving inorganic iron or arsenic preparations.

2. Iron and arsenic preparations exercise practically no beneficial effect in correcting secondary anemias.

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STUDIES IN CALCIUM AND BLOOD COAGULATION. (WITH SPECIAL REFERENCE TO THE USE OF SALTED PLASMA AS A METHOD OF ESTIMATING CLOTTING TIME.)

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The methods, which have been described for the determination of the clotting time of the blood, may be placed in two well-defined groups. In the first group the coagulation time of the whole blood is measured directly. The method outlined by Lee and White[1] calls for blood obtained directly from a vein and collected into a small test-tube of a definite size. Of the methods reported by Hinman and Sladen[2] and Solis-Cohen,[3] the greater number use blood obtained by ear or finger puncture, the differences in procedure usually depending upon some specially designed receptacle, or the adoption of a novel departure in defining the coagulation point. In all of these despite the refinement of the coagulometer, lies the fundamental objection of inherent errors accompanying methods by which blood is obtained from puncture wounds. Again, no method of this group throws any light upon the individual factors involved in the process.

In the second group fall those methods in which clotting is first inhibited through the agency of some anticoagulant salt, to be restored later either by recalcification or diluting with water. Howell's method[4] for the determination of prothrombin time, exemplifies this group inasmuch as clotting is first suspended by sodium oxalate and after centrifugalization the plasma is recalcified so that coagulation proceeds once more. In Gram's modification[5] of this method the citrate is substituted for the oxalate. Brissaud[6] utilizes hypertonic sodium chloride as the anticoagulant and by dilution effects a return of coagulation. With Howell's method[4] the prothrombin factor is investigated incidental to determining the coagulation time, while this paper will consider the calcium factor in its relation to clotting.

The method employed in these studies is based on the well-known observation that hypertonic sodium chloride prevents coagulation of blood in vitro and that by dilution with water this property is restored. It is interesting to note in this connection that Velden[7] and Schenk[8] have observed that concentrated sodium chloride solution intravenously administered hastens blood coagulation, a marked parallelism in this respect to the action of sodium citrate as described by Weil.[9]

In his experiments on the determination of clotting time, Bris-

saud[6] employed distilled water for the restitution of clotting in salted plasma. In adapting this method for more practical clinical use, the plan suggested itself of comparing the rate of coagulation in the salted plasma diluted with distilled water, with that in which the diluting fluid consists of water containing minute traces of calcium chloride in known concentration in order to study the influence of this salt upon coagulation time.

The Method. The blood* is collected in special test tubes graduated to 5 cc. This tube has an inside diameter of 1 cm. and a length of 7.5 cm. Similar tubes are used in the test. All of the tubes are carefully cleaned in bichromate-sulphuric acid mixture and washed thoroughly in distilled water. A pipette is constructed of glass tubing having a diameter of from 0.5 to 0.6 cm., the capillary end of which has a bore less than 1 mm. in diameter, and to the wide end a rubber nipple is attached.

A hypertonic solution of sodium chloride is prepared by dissolving 10 gm. of calcium free salt in 100 cc of distilled water. The most uniform results are obtained when this solution is from one to six weeks old. For reasons at present unknown fresher solutions prolong clotting time and older ones shorten it. Calcium chloride solutions of two strengths are used, 1 to 10,000 and 1 to 2,000 prepared by dilution of a 1 per cent stock solution of anhydrous calcium chloride.

With a sterile 10-cc syringe, blood is withdrawn by vena puncture and 4 cc are immediately placed in the graduated test tube which contains 1 cc of the 10 per cent sodium chloride solution.† The tube is closed with a paraffined cork and the contents mixed by rapid inversion. In each of 5 test tubes of the same type, previously rinsed with physiological salt solution, 1 cc of blood is placed and the coagulation time is determined by the direct method of Lee and White.[1] The salted blood is centrifuged in its container for exactly five minutes at a speed of from 1000 to 1300 revolutions. Three rows of four standard tubes each are placed in a rack, and in each tube there are placed 5 drops of the supernatant salted plasma. With the same pipette there are added to the first row, 5–6–7–8 drops of distilled water; in the second row a similar number of drops of the 1 to 10,000 calcium chloride solution and in the third the same amounts of the 1 to 2000 solution. It is essential to shake the tubes after the addition of each diluent. The final dilutions of sodium chloride in each tube therefore ranges between 1 per cent for the tube that has received 5 drops and 0.77 per cent for the one with 8 drops.

* In all cases, blood was obtained before breakfast.

† Ten per cent sodium chloride diluted to 2 per cent with 4 volumes of blood has been found superior to the 20 per cent solution reduced to 5 per cent as prescribed by Brissaud.[6] The lower concentration of the salt while as efficient in inhibiting clotting, is more satisfactory than the stronger solution in that hemolysis is obviated.

All the tests were conducted at room temperatures, between 21 to 24° C. In order to obtain the most uniform results, it is necessary that the interval between salting the blood and the beginning of centrifugalization should not exceed ten minutes; that after the supernatant plasma is removed the test should be completed within five minutes so that the entire period elapsing from the time the blood leaves the vein until the completion of the recalcification should not exceed twenty minutes.

As set forth by Addis[10] in the accurate estimation of coagulation time, the end-point must be clear and definite and always indicate the same degree of coagulation. These requisites are met with in the use of salted plasma. In the test, the time of dilution is carefully noted for each set of tubes. The latter remain undisturbed for five minutes, when the rack is raised and tilted slightly to observe the inception of clotting. This is repeated at the end of every minute thereafter, until coagulation has been completed in all the tubes, the readings being recorded as clotting takes place in the individual tube. Clotting progresses gradually through various stages of increasing turbidity and diminished fluidity to its termination. The most intense turbidity is observed in the mixtures containing the larger quantities as well as the more concentrated calcium solutions. The end-point is reached when the clot is firm and upon inverting the tube the meniscus of the coagulum remains immobile.

A protocol of a single test will serve to emphasize its salient features:

Normal Case:

	Diluting agent.		
	Distilled Water.	Calcium chlorid.	
Five drops of salted plasma, plus	(coagulation time in minutes.)	1 to 10,000	1 to 2000
5 drops	25	19	14
6 drops	20	14	12
7 drops	20	14	11
8 drops	15	10	8
Average coagulation time	20	14	11

Temperature, 24° C.

In recording the results the method adopted was to note the figures comprising the average coagulation time with each diluent, in this case—twenty, fourteen, and eleven minutes respectively.

Discussion. The mechanism by which hypertonic salt solution inhibits coagulation is as yet a matter of conjecture. Lee and Vincent[11] offer evidence to show that concentrated solutions of sodium chloride prevent the formation of thrombin. Howell[12] states that calcium is deviated so that it cannot activate prothrombin. One is impressed constantly in studying the coagulation process that the changes involved conform to the laws of colloids and that these laws are obeyed when blood is mixed in vitro with hypertonic sodium chloride and later diluted to isotonic strength.

The inhibition of coagulation by this salt according to Pickering and Hewitt[13] is due to the relatively stable unions of the proteins with the added electrolytes and to some extent also to the withdrawal of water. On dilution, with the reduced concentrations of the electrolytes the coagulation process once more manifests itself. The precise fate of the calcium during this process is problematical. From the observations made in the course of these studies, the only conclusions that can definitely be drawn are that upon rendering salted plasma isotonic, coagulation is restored and that with the further addition of minute traces of calcium chloride it is greatly accelerated.

It is generally accepted that calcium in common with the other inorganic bases of blood serum may exist in at least two forms: in the diffusible and potentially ionizable state and in the non-ionizable combination with serum proteins. Of the total calcium present in serum, von Meysenburg, Pappenheimer, Zucker and Murray[14] found 60 to 70 per cent to be diffusible while Neuhausen and Marshall[15] determined that even a smaller fraction (about 10 per cent) was present in ionizable form. In view of the incompleteness of knowledge concerning the individual roles of diffusible and ionic calcium in the coagulation of blood, the term available calcium will be substituted in contradistinction to the non-available protein-bound calcium.

A possible explanation of the action of hypertonic sodium chloride solution is that upon its admixture with blood in the concentration stated above, sufficient calcium is inactivated to aid in the suppression of clotting and that on dilution with water a considerable portion of this substance is once more brought into play in its available form. The well-known antagonism existing between sodium and calcium salts in physiological processes is pertinent at this point and has recently been described by Lillie[16] in its application to fundamental biological relationships. Clowes[17] extends this principle of antagonism into the province of blood coagulation since "the salts of calcium tend to promote and alkalies and salts of sodium to inhibit the reversal or transposition of phase relations of a protein sol like blood plasma into a jelly like blood clot." Novi[18] refers to the "decalcifying" action of sodium chloride upon tissues. Budde and Freudenberg[19] discussing the ionization of calcium in solutions containing the inorganic constituents of blood suggest that the addition of sodium chloride depresses the dissociation of calcium through the preponderance of chlorine ions.

In many respects the behavior of the citrate of sodium must be akin to that of its chloride particularly with respect to the influence of the common cation sodium. Sodium citrate according to Sabbatini[20] inhibits coagulation not by precipitating the calcium but by checking its ionization hence rendering it unavailable for blood clotting. From this conception Bloch[21] has evolved a theory of

coagulation based principally upon the alteration in the activity of calcium. That the evidence thus offered although largely indirect is relevant to the suspension of blood coagulation by hypertonic sodium chloride, is extremely probable but that the calcium alone is the sole factor in a process involving the interaction of so many elements requires added proof.

In rendering salted plasma isotonic with distilled water, the dissociation of calcium compounds proceeds, and available calcium is once more present for clotting. Whatever loss in concentration or activity of available calcium is sustained by salting is replaced by reinforcement with calcium chloride solutions of the two strengths designated in the procedure.

Increasing Concentrations of Calcium Chloride and the Clotting of Salted Plasma. The effect upon coagulation time of diluting salted plasma with calcium chloride solutions of increasing concentrations is illustrated in the following experiment:

Normal Case:

	Diluting agent.					
		Calcium chloride solutions.				
	Distilled water.	1–10,000	1–2000	1–1000	1–200	1–100
Average coagulation time in minutes	20	16	10	12	27	105

Temperature, 22° C.

Similar observations have been reported by Heard[22], who found that calcium in common with the cations of the other alkaline earths and the metals, retard clotting with the higher concentrations. The first two concentrations of calcium chloride noted in the table, were, therefore, chosen as the optimum for diluting salted plasma.

The Influence of the Interval between the Salting of Blood and its Centrifugalization upon Clotting. As stated in the discussion of the method, it was found necessary to limit the period between the collection of the blood and its salting on the one hand, and the centrifugalization of the mixture on the other to ten minutes. The necessity for this limitation was originally observed in carrying out prothrombin determinations according to the method of Howell,[4] in which it soon became evident that as this period was prolonged, the coagulation time was proportionally shortened. Rosenthal and Baehr[23] noted like findings in studying the effect of the intravenous administration of sodium citrate upon prothrombin time. An illustration of how this influence operates with salted plasma is recorded in the following experiment:

Normal Case:

	Diluting agent.		
		Calcium chloride.	
Interval between salting of blood and centrifuging.	Distilled water.	1 to 10,000 (average coagulation time in minutes.)	1 to 2000
10 minutes	23	15	10
25 minutes	21	11	8
40 minutes	16	7	6

Temperature, 22°.

TABLE I.—SERIES OF NORMAL CASES.

Case number.	Diluting agent.				
	Distilled water.	Calcium chloride.		Direct Cong. time.	Serum calcium.
		1 to 10,000	1 to 2000		
	(average coagulation time in minutes.)				
1	17	11	8	8	
2	21	15	13	10	
3	17	17	12	10	
4	18	13	11	7	
5	25	13	9	10	
6	18	14	10	6	10.0
7	20	14	11	10	10.7
8	20	14	11	11	9.7
9	18	16	9	7	10.1
10	20	16	10	5	10.3
11	27	14	11	8	11.7
12	23	15	10	9	10.1
Average	20	14	10	8	10.8
High	27	17	13	11	11.7
Low	17	11	8	5	9.7

Clotting of Salted Plasma in Normal Cases (Table I).—The series of normal cases comprises, in the main, minor surgical conditions in which an opportunity was afforded to observe the extent of bleeding, and where there was no reason to expect any deviation from normal coagulation time. It is apparent from Table I, that the widest variation occurs with distilled water as the diluting agent. With calcium chloride, however, the range for clotting time becomes much more limited. With the direct method of Lee and White,[1] the results of which are recorded in the table, there occasionally occur marked variations in the clotting time among the five tubes. This finding led to the use of this number of tubes for the test instead of but one as is sometimes the practice. In Table I the values for this method represent average results, the determinations for clotting time being discarded in a tube in which there was an unwarranted prolongation. Such differences are singular in view of the simplicity of the entire procedure, and the attention paid to the elimination of a number of extrinsic factors.

Clotting of Salted Plasma in Pathological Conditions. 1. *Jaundice* (Table II). The exact part that calcium plays in jaundice is as yet unsettled. King and Stewart[24] and King, Bigelow and Pearce[25] found that in experimentally produced jaundice in dogs, the calcium content of the blood was increased. This was interpreted by them as a protective mechanism against the circulatory pigments of obstructive jaundice, since combinations of calcium and the pigment proved to be less toxic than the uncombined pigment. In the 4 cases of jaundice reported by Halverson, Mohler and Bergeim,[26] no increase in calcium values was obtained and in 1 there was a definite decrease.

With the knowledge that jaundice is frequently accompanied by the hemorrhagic tendency, it was considered opportune to study

this condition not alone with reference to clotting time but also to the calcium and bilirubin content of the blood serum, for which new methods have recently been developed. A series of ten cases was, therefore, investigated and in these the serum calcium was determined by the method of Kramer and Tisdall,[27] and the icterus index by Bernhard and Maue's modification of Meulengracht's method described by Maue[28] and Stetten.[29] At the same time, clotting time was determined on the salted plasma and by the direct method of Lee and White.[1]

The determinations on the salted plasma gave definitely prolonged clotting time in 6 cases, and in 5 using the direct method. With the latter a clotting time of twelve minutes or over was regarded as delayed. Case 5 showed delayed clotting with the direct method and normal time with the salted plasma, but at operation no oozing was encountered. Cases 2 and 8 gave delayed coagulation with the salted plasma, and high normal clotting time values with the direct method.

In none of the cases of this series was the serum calcium increased. In Cases 1 and 8, the serum calcium was materially reduced and coagulation prolonged. It is obvious, however, that in this group of cases, no definite parallelism exists between serum calcium content, the depth of jaundice and clotting time. In the two cases just cited with the lowest calcium values, the most intense degrees of jaundice, as measured by the icterus index, were not present. On the contrary, the highest index (Case 7) occurred in combination with a normal calcium and only a slight retardation in clotting. Again, the greatest delay in coagulation was observed in a case of obstructive jaundice (Case 6), with an index of 115 and a normal serum calcium.

Concerning the influence of the duration of jaundice upon clotting time and serum calcium, it is hazardous to venture a definite statement since the accurate onset of jaundice is subject to varied personal interpretation. Mindful of the shortcomings of this information, it is interesting, nevertheless, to note the discrepancy between the duration of jaundice and coagulation time. These findings are in accordance with those of Morawitz and Bierich,[30] who concluded that altered coagulation in cholemia was independent of the duration or intensity of the jaundice.

Lee and Vincent[31] ascribe the delay in coagulation of blood in certain cases of obstructive jaundice to a lack of available calcium. In a case with a normal serum calcium and delayed coagulation, there are the possibilities that the available calcium fraction may be low or that the other factors involved in clotting of blood may be at fault.

With salted plasma, the effect of diluting with calcium chloride solutions is in general to hasten coagulation. In three instances (Cases 1, 4, 8) this acceleration was unusually pronounced and

TABLE II.—SERIES OF JAUNDICE CASES.

Case number.	History number.	Diagnosis.	Diluting agent.			Direct coagulation time.	Icterus index.	Serum calcium.	Duration of jaundice. (from onset to test)
			Distilled water. (average coa	Calcium chloride. 1 to 10,000 gulation time	Calcium chloride. 1 to 2000 in minutes.)				
1 . . .	2981	Carcinoma of head of pancreas	51	28	19	12	47	8.5	Six days.
2 . . .	3505	Carcinoma of head of pancreas	34	17	12	10	75	9.2	Two and one-half months.
3 . . .	3085	Carcinoma of gall-bladder	21	15	12	8	50	11.2	Two months.
4 . . .	3833	Cholelithiasis	70*	24	15	14	110	9.7	Six months.
5 . . .	3211	Cholelithiasis	22	11	8	12	32	11.3	Two weeks.
6 . . .	5009	Cholelithiasis	0‡	55*	37	25	115	10.0	Nine weeks.
7 . . .	4034	Catarrhal jaundice	30	20	13	11	140	10.0	Six days.
8 . . .	4759	Catarrhal jaundice	34†	19	13	11	100	7.4	One and one-half months.
9 . . .	4403	Catarrhal jaundice	22	15	10	8	116	9.0	Twelve days.
10 . . .	4757	Syphilis of liver	40	32	24	15	136	10.0	Eight days.

* No coagulation in tube with 5 drops of diluting agent.
† No coagulation in tubes with 5 and 6 drops of diluting agent.
‡ No coagulation in any of the tubes.
Normal icterus index below 6.0.

probably indicates a lack of available calcium. In contrast to these, Case 6 reveals no such decided change in clotting time, findings which speak for the other elements of clotting as fibrinogen or thrombin as the factors responsible for prolonging coagulation. In this connection, therefore, the use of salted plasma as a method for estimating coagulation time may provide a means for determining preoperatively the need for available calcium and its therapeutic administration, a procedure comparable in this respect to the "calcium in vitro" test described by Lee and Vincent.[31]

2. *Nephritis* (Table III).

The small series of cases of nephritis from the miscellaneous group offers several features of interest. Salvesen and Linder[32] have demonstrated that the decrease in serum calcium in nephritis, may be accounted for by the fall in plasma proteins which exist in combination with the non-diffusible calcium component. The values recorded in Table III, in general corroborate this decrease, save in one instance (Case 4) in which the serum calcium was even lower than a theoretical loss of the entire quota of non-diffusible calcium would warrant. This probably represents an encroachment upon the diffusible and ionizable calcium fraction. The patient in this case exhibited signs of increased excitability manifested by tremors of the face and hands, indications fundamentally of a deficiency of calcium ions. Some of the nervous disturbances of uremia, De Wesselow[33] correlates with low calcium values.

The coagulation time in these cases of nephritis does not run parallel with the serum calcium. This can be explained, however, on the basis that the decreased calcium, although representing a loss in the non-diffusible fraction, is normal at any rate with respect to its diffusible and ionizable form, in quantities sufficient at least not only to prevent the nervous symptoms, but to maintain a normal coagulation time. In the nephritics with the prolonged clotting time, there was in the one (Case 4) a probable deficiency in the available calcium, and in the other (Case 6*b*) a profound secondary anemia as a complicating factor. With the former the lowest calcium in the series (4.1 mg.) was obtained, and here the addition of solutions of calcium chloride to render the salted plasma isotonic produced a most marked acceleration in clotting time.

It may be assumed, then, that both the coagulation of blood and the absence of some of the nervous manifestations in nephritis are dependent upon an adequate supply of calcium ions. It remains to be seen, however, whether the calcium ions in coagulation and in the nephritic process are identical. If they are, it is possible that a marked acceleration in clotting time in a case of nephritis (Case 4), in the tubes in which calcium chloride is used to dilute the salted plasma, as compared with that using distilled water, may serve to indicate a deficiency in available calcium and a guide to the advisability of instituting calcium therapy.

TABLE III.—SERIES OF MISCELLANEOUS CASES.

Case No.	Hist. No.	Diagnosis.	Diluting agent.			Direct coag. time.	Serum calcium.
				Calcium chloride.			
			Dist. water. (average	1-10,000 coagulation	1-2000 time in minutes.)		
1 . .	4568	Hemiplegia	11	6	5	7	11.3
2 . .	3613	Hemophilia	0*	3 hrs. 33 min.†	4 hrs. 17 min.	4 hrs. 25 min.	10.2
3 . .	4619	Pulmonary tuberculosis	32	22	14	12	8.9
4 . .	4944	Chronic nephritis; uremic twitchings 24 hours before death	43	14	14	19	4.1
5 . .	4437	Chronic nephritis; uremia; coma	21	15	8	7	7.8
6 . .	4796	Acute nephritis;	(*a*) 29	15	14	13	7.2
		three weeks later, hematuria and secondary anemia;	(*b*) 32	23	19	18	7.8
		after two transfusions, marked improvement in blood and kidney function	(*c*) 24	22	15	13	9.0
7 . .	4745	Chronic nephritis; marked hemorrhage, 6 days after transfusion;	(*a*) 22	19	16	12	9.5
		16 days after transfusion	(*b*) 23	13	9	9	8.5

* No coagulation in any of the tubes.
† No coagulation in tubes with 5 and 6 drops of diluting agent.

Summary. 1. A method for estimating coagulation time is described in which blood is salted with hypertonic sodium chloride. The coagulation time is determined after diluting the salted plasma with distilled water as well as with calcium chloride of two concentrations.

2. In carrying out this method certain restrictions must be borne in mind, such as the period elapsing between the salting of the blood and its centrifugalization, the age of the hypertonic sodium chloride solution, and the temperature at which the tests are conducted.

3. The clotting time by this method is compared with that of Lee and White in a series of normal cases, in jaundice, and in nephritis.

In the three groups the serum calcium content is also determined, together with the icterus index in jaundice.

4. It may be possible to employ this method in jaundice, as a means of determining preoperatively the effect upon clotting time of the administration of calcium, similar to the "calcium in vitro" test of Lee and Vincent.

Conclusions. 1. In the process of blood clotting, the calcium principally involved is its ionizable and available form.

2. Hypertonic sodium chloride of the strength used in the test, probably exerts an effect upon all the elements essential to coagulation and in the case of calcium resulting in its inactivation.

3. With increasing concentrations of calcium chloride in the dilution of salted plasma a gradual retardation of clotting time is observed.

4. As the period between the salting of the blood and its subsequent centrifugalization is increased, the clotting time of the salted plasma after dilution is shortened.

5. The clotting time in jaundice may be normal, but when delayed it does not run parallel with the intensity or period of duration of this condition.

6. In nephritis, a consideration of the clotting time also necessitates the differentiation between available and non-available or protein-bound calcium.

In conclusion, mention must be made of the shortcomings inherent in every method for the determination of clotting time, due to the complexity of the process. As pointed out, even so simple a method as the direct one may yield marked variations in clotting time in the several tubes employed in the test. It is impossible to state definitely the clotting time in a specified pathological condition without a large number of determinations, since individual cases present peculiar features which play a role in coagulation.

I wish to express my indebtedness to Adolph Bernhard, pathological chemist to this hospital, whose many kind suggestions and technical aid facilitated this study.

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A CLINICAL, PATHOLOGICAL AND OPERATIVE STUDY OF THE ICTERUS INDEX.

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Clinicians are showing a markedly increased interest in the study of diagnostic methods meant to increase our knowledge of the function of the liver. Widal has attacked the problem by noting the behavior of the leukocytes after food ingestion. The normal acting liver seems to provide for a digestion leukocytosis. In certain hepatic dysfunction there is a digestive leukopenia.

More recently a number of workers[1] have utilized the behavior of bile pigments as a basis for determining the degree of liver function. Bile pigments are essentially formed from the destruction of hemoglobin, probably within the liver. However, the amount of pigment does not necessarily depend on the amount of hemoglobin destroyed. In certain cases the excreted bilirubin would undoubtedly require a complete depletion of the red cells from the serum in order to supply this excreted pigment. There must then be some additional source of pigment production. However, the liver is the most essential organ in the production of bile pigment. Hence the interpretation of the behavior of bilirubin in the blood serum

becomes the chief aim in the study of liver function. Since the destruction of hemoglobin is a continual physiological process,[6] we must expect a certain constant of bilirubin in the normal blood serum. That normal range has been placed at approximately 1 part of bilirubin to 500,000 or 600,000 parts of serum.

When the concentration of this pigment in the blood has increased to approximately 1 part in 50,000 or 60,000 the tissue cells begin to show a visible saturation or tinging of bile and macroscopical or clinical jaundice is apparent. This range of bilirubinemia between the normal and macroscopic tinging has been termed "latent jaundice."

To determine the clinical value of the measurement of this stage is the purpose of this report.

Alice R. Bernheim[3] has used the colorimeter to measure the degree of bilirubinemia in various clinical conditions, and has aptly termed this measurement the "icterus index." Following her method, the authors have carefully checked a well-studied group of cases, and have tabulated this work for further observation and study by others. Our work agrees with hers that there is a measurable and fairly constant quantity of bilirubin in the serum of the same individual normally from day to day. This serum pigment is undoubtedly quantitatively increased by such diseases as:

1. The hemolytic processes of the body, as pernicious anemia, hemolytic jaundice, hematomas, a ruptured viscus with extravasation of blood and such diseases as cardiac decompensation, pneumonia and malaria.

2. Disturbances of the biliary system, as cholecystitis, cholelithiasis, cholangitis, certain adhesions about the gall bladder and diseases of the liver involving the bile ducts.

We are in accord with Bernheim that the normal range is between 4 and 6 and that the range of "latent jaundice" lies between 6 and 15. Above 15 clinical jaundice usually begins to appear.

Van den Bergh,[1] using the Diazo reaction, attempts to work out a test that will differentiate the obstructive from the hemolytic type of jaundice. He contends that in the former condition bile is free and readily demonstrable by the test, while in the latter state the pigment is attached to certain albuminous bodies and must be liberated by means of alcohol before it can be detected. This test is only qualitative, however, and the accuracy of its differentiation has still to be carefully checked.

J. C. Friedman[5] has reported admirably a number of cases in which he used Fouchet's test for the detection of bile pigment in the serum. While this test seems to be specific for bilirubin, it furnishes no means of measuring the intensity of the reaction. He has demonstrated that a positive test may be present during attacks of cholecystitis, and negative in the interval, which is in harmony

with the influence such attacks would have on liver function. A test, positive during a gall bladder attack, remains positive for some time after the diseased condition has subsided. We, therefore, believe we are warranted clinically to consider nearly every case of cholecystitis as an ascending infection. The resultant hyperbilirubinemia then becomes a more probable index to a disturbed liver function; by converse reasoning an encountered bilirubinemia with clinical gall bladder findings becomes a much stronger diagnostic basis for cholecystitis.

Speik, Liljedahl and Folk[4] have recently applied Fouchet's test to a considerable group of patients. Of 40 cases, clinically and roentgenologically (and some by operative procedure) diagnosed cholecystitis, only 27 gave a positive reaction. They are at variance with practically all other observers in finding that the anemia of malnutrition—secondary in type and without other pathological findings—often has a slight increase over the normal in the bilirubin content of serum.

The primary anemias logically produce icteric sera, while those secondary in type have too low a rate of red blood cell destruction to raise the bilirubinemia to normal.

On page 586 we wish to reproduce Bernheim's chart and follow it with our own.

Previously Barrow and Franklin[7] have pointed out the constancy, diagnostic and prognostic value of the Widal hemoclastic crisis test in typhoid fever. The icterus index runs parallel to this test in the same disease. These tests further confirm the belief that typhoid fever produces excessive biliary strain. Consequently, by their use we are able to measure a fair degree of liver function in this and other diseases. These two tests explain Ehrlich's Diazo reaction in the urine of typhoid patients. The variable degree of excretion or filtration of bilirubin through the kidneys, together with the degree of concentration in the serum, explains its value and variation as a test for typhoid fever. We know that certain cases may have a very high concentration of bile in the blood before the tissues take on the icteric tinge. It is probable that kidney excretion or filtration does not begin until this stage of tissue saturation is present. The determination of the icterus index and the "hemoclastic crisis" are relatively of very much more value in the diagnosis of typhoid fever than the Diazo reaction in the urine.

In the absence of any accountable pyogenic complication it has been generally observed that hyperbilirubinemia is accompanied by a leukopenia. It seems fair to suspect that bilirubin may have a direct relation to, or action upon, the white cell producing mechanism of the body. The leukopenia of both malaria and typhoid fever is readily explained by the presence of excess bile in the blood.

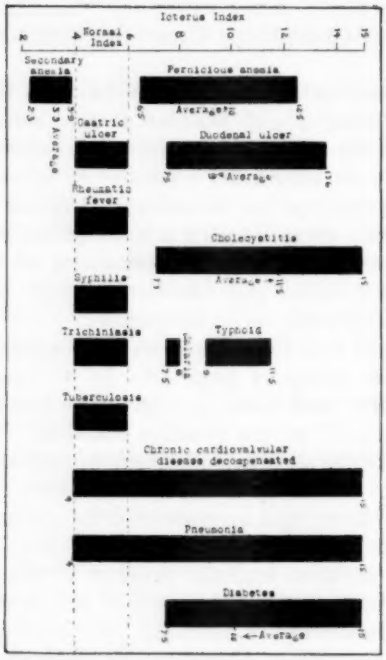

CHART I.—Icterus index in various diseases.

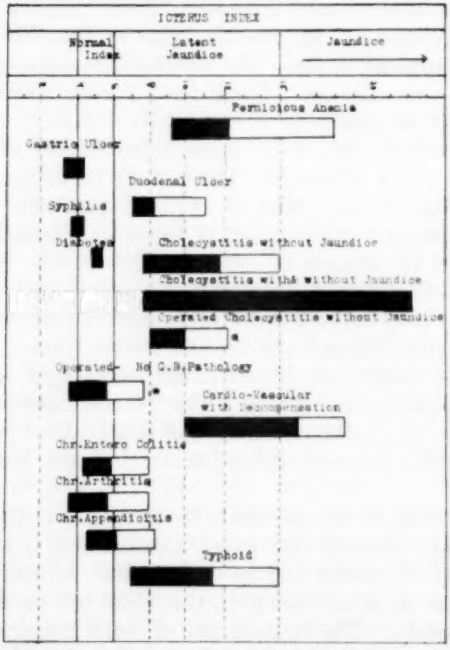

CHART II.—Solid black indicates the reading from the minimum to the average. Unfilled space indicates maximum reading of these cases. Jaundice did not necessarily occur when the reading reached fifteen. It did not occur with reading below fifteen.

Below is the tabulation of 24 cases of typhoid fever from the General Hospital service.

TABLE I.

No.	White.	Red's.	Hemoglobin.	Widal hemoclastic.	Widal.	Icterus index.
1	3150	3,100,000	70	Positive	Positive	7.0
2	3900	3,950,000	75	Positive	Negative	5.0
3	2800	3,100,000	80	Positive	Positive	9.0
4	4750	4,250,000	80	Positive	Positive	10.0
5	3500	4,150,000	85	Positive	Positive	4.5
6	4500	3,750,000	65	Positive	Positive	7.0
7	6400	4,500,000	75	Negative	Positive	5.2
8	7450	4,250,000	90	Positive	Positive	10.0
9	5400	3,100,000	80	Positive	Positive	9.0
10	8500	4,150,000	85	Positive	Positive	6.8
11	4950	3,950,000	75	Positive	Positive	8.8
12	5350	4,750,000	75	Positive	Positive	8.6
13	8250	4,350,000	85	Positive	Positive	10.0
14	5600	4,750,000	85	Negative	Positive	9.3
15	6850	4,600,000	75	Positive	Negative	10.0
16*	2700	4,050,000	70	Negative	Negative	15.0
17	5200	3,740,000	65	Positive	Positive	15.0
18	6800	4,250,000	80	Positive	Negative	10.0
19	4000	4,150,000	80	Positive	Positive	10.0
20	8050	4,250,000	85	Positive	Positive	5.0
21	5600	4,050,000	70	Negative	Positive	9.3
22	6550	3,250,000	75	Positive	Positive	7.5
23	3150	3,750,000	65	Positive	Positive	15.0
24	5300	3,950,000	80	Negative	Positive	15.0

* Case No. 16 was clinically typhoid and the typhoid bacillus was recovered from the stool by culture.

Nos. 2, 5 and 7 had the icterus index taken after intestinal hemorrhages.

The blood nitrogen in these cases was slightly above normal. The Diazo reaction of the urine cannot be averaged. The icterus index averaged nearly 12. There was no visible jaundice. The hemoclastic crisis was positive in 19 cases, or 80 per cent. The serum Widal was positive in 20 cases, or 81 per cent. The icterus index and the "hemoclastic" test are of value in diagnosis, prognosis and certain forms of treatment. Schamberg[2] has used the former as a guide to the administration of neoarsphenamine.

Certain of our cases presented much difficulty in differential diagnosis. The value of this test is shown by the following cases, each representing a general group:

Case Reports. CASE I.—Mrs. H. T. complained of sporadic attacks of indigestion. There had been a periodic diarrhea and alternating constipation for over a year. Certain foods distressed her but she could not tell which ones were at fault. There were frequent cramp-like pains variously ascribed to the colon, the appendix and gall bladder region. The usual cervical and back pains were present. Examination showed a low blood pressure; temperature, 99.2°; severely tender cecum; no tenderness over the gall bladder; white blood cells, 10,200; polymorphonuclears, 60 per cent; Ameba histolytica, spirillæ and triple plus fatty crystals

in the stool. The icterus index was 5.6. At operation a chronic appendix was found. The gall bladder was normal in every respect externally, and by its bile content and mucosa was not diseased, but it contained two unobstructing gall stones. Recovery was uneventful.

CASE II.—Mr. P. D. S. complained of blind and dizzy spells, no energy and much headache. This condition obtained for about three years. There were attacks of indigestion and extreme hyperacidity, much colon gas and a very tender epigastrium. Food did not relieve the indigestion. The bowels were fairly regular. Weight loss, 15 pounds; blood-pressure low, 100/70; temperature, 99.2°. Pain and tenderness on pressure was about equal over the gall bladder, cecum and sigmoid. White blood cells, 8200; polymorphonuclears, 56 per cent; mononuclears, 44 per cent; stools show blastocystis, chilomastix, spirillæ and fatty crystals. The stomach showed fair motility and no blood; free hydrochloric acid, 58 per cent, combined, 18 per cent, total, 76 per cent. Under treatment the patient became much better for one year, then relapsed. Icterus index before operation was 5. Operation showed a bad chronic appendix and a normal gall bladder. Convalescence uneventful and recovery splendid.

CASE III.—Mrs. R. W. L. complained of a constant and annoying pain in the right side; at times food distressed but never relieved her; soda did not help. At times there was nausea and vomiting but never any fever; severe headaches accompanied these attacks, which were worse at night. There were periodic attacks of cystitis. She never had typhoid or any serious illness before. Skin had icteric tint, but no definite jaundice. Blood-pressure, 110/80; temperature, 99°. The three points of abdominal tenderness were the gall bladder region, cecum and lower descending colon. Tenderness over the gall bladder and lower colon was about equal. White blood cells, 10,600; polymorphonuclears, 77 per cent; mononuclears, 23 per cent; stool has blastocystis and chilomastix cysts and fatty crystals; icterus index, 26.6. Diagnosis: Chronic cholecystitis and chronic enterocolitis. Operation: Gall stones removed and drainage. Appendix was normal. One week later the icterus had returned to normal. Recovery and convalescence satisfactory.

CASE IV.—Mr. N. R. M. came to the office with a severe mental depression, some nausea and extreme tiredness. During attacks of nausea the heart became very irregular and weak, and collapse was imminent. The teeth and tonsils were cared for; chest negative; upper right quadrant of abdomen only slightly rigid, but not tender. Examination showed hemoglobin, 70 per cent; red blood cells, 4,260,000; white blood cells, 6600; polymorphonuclears, 54 per cent; mononuclears, 46 per cent; stool showed Ameba histolytica, fatty crystals, chilomastix and spirillæ. Icterus index on

May 21, 1924, was 24.6. Skin showed definite icteric tinge. The diagnosis of acute cholangitis, probably amebic, was made. He was placed on rigid colon treatment, and in three weeks his symptoms were very greatly relieved. On June 21, 1924, his icterus index had returned to 6, and he has remained in good condition since.

CASE V.—Mrs. R. E. had been suffering from periodic attacks of bronchitis, with temporary smothering spells due to heart weakness. These attacks were associated with indigestion and constipation and on two occasions by a bronchial pneumonia. During her last attack the heart became very irregular and weak, with edema of the lungs and general liver engorgement. The skin was very icteric. Her blood was hemoglobin, 80 per cent; red blood cells, 4,050,000; white blood cells, 6600; polymorphonuclears, 59 per cent; mononuclears, 34 per cent; transitionals, 7 per cent. The chest showed considerable edema of the lungs, a markedly dilated right heart with very irregular weak tones. The liver was large and tender. The bowels constipated. The icterus index was 20. After rest in bed, digitalis and general treatment, the heart tones became normal and the liver reduced greatly in size. The icterus index dropped to 9.8. The roentgen-ray demonstrated a very large heart and a pathological gall bladder.

The following tables shows a small group of cases operated upon after having the test applied as an aid in diagnosis:

TABLE II.—POSITIVE FOR GALL BLADDER.

No.	Icterus index.	Roentgen-ray.	Diagnosis.	Operative findings.
7	9.5	Pathological gall bladder	Chronic cholecystitis; chronic enterocolitis	Pathological gall bladder.
8	64.0	.....	Acute cholecystitis	Pathological gall bladder.
9	12.5	Pathological gall bladder	Chronic cholecystitis; chronic arthritis; chronic enterocolitis	Pathological gall bladder.
10	25.0	None	Cholelithiasis; cystitis cancer bowel	Pathological gall bladder and stone; cancer bowel.
19	8.0	Pathological gall bladder	Pathological gall bladder; hemorrhagic pleurisy	Adhesions around gall bladder interfering with drainage.
49	10.0	Duodenal ulcer; pathological gall bladder	Duodenal ulcer; pathological gall bladder; chronic enterocolitis	Duodenal ulcer; pathological gallbladder.
28	26.6	Pathological gall bladder	Pathological gall bladder; chronic appendix	Pathological gall bladder only.
53	50.0	.....	Cancer head pancreas; Cancer bile duct	Died. Autopsy proved findings pathological gall-bladder.
80	15.0 *7.6	Pathological gall bladder	Duodenal ulcer and adhesions	Duodenal ulcers; adhesions; inflamed gall bladder.

* No. 80 dropped to 7.6 on the fifth day after operation.

TABLE III.—NEGATIVE FOR GALL BLADDER.

No.	Icterus index.	Roentgen-ray.	Diagnosis.	Operative findings.
31	5.4	Pathological gall bladder	Toxic thyroid; chronic enterocolitis; fibroid tumor	Gall bladder normal; uterine fibroids.
47	7.4	Pathological gall bladder; duodenal ulcer	Duodenal ulcer; chronic colitis, colon stasis, chronic appendix	Chronic appendicitis; adhesions.
52	3.4	Gastric ulcer; pathological gall bladder	Chronic enterocolitis; gastric ulcer adhesions	Gastric ulcer; adhesions around gall bladder; gall bladder normal.
57	5.6	Gastric ulcer, colon stasis and adhesions; pathological gall bladder	Chronic arthritis; acute bronchitis; chronic enterocolitis	Gall bladder normal; pyloric stenosis; adhesions.
81	5.0	.....	Chronic appendix; chronic enterocolitis	Gall bladder normal; chronic appendix.
66	6.0	Duodenal ulcer	Ruptured appendix	Appendicitis, otherwise O.K.
67	7.8	Gall bladder normal	Chronic appendix; double hydrosalpinx	Chronic appendicitis salpingitis.
68	6.4	Chronic appendix; colon stasis and adhesions	Chronic appendix; colon adhesions	Chronic appendicitis; adhesions.
11	5.4	Gall bladder and appendix	Gall bladder and appendix	Gall stones and appendix; gall bladder negative.
12	6.0	Gall bladder and duodenal ulcer	Appendix	Subacute appendicitis.
63	8.2	Colon stasis with adhesions	Chronic arthritis; chronic appendix; colon stasis	Chronic appendix; gall bladder normal.
65	7.0	Colon stasis with adhesions	Chronic appendix; chronic enterocolitis	Chronic appendix; ovarian cysts; gall bladder normal.
78	5.4	.....	Chronic appendix	Gall stones, gall bladder normal in color. Bile normal in color. No infection.
79	6.2	Gall bladder normal; chronic appendix	Chronic appendix	Chronic appendix; gall bladder normal.

In our greater table that follows we desire to call attention to the fact that the blood nitrogen in these cases was not an instructive factor. There is only 1 luetic case (No. 71) in the entire group. Icterus began to appear clinically in nearly all cases when the index rose above 15. However, in some there was no visible jaundice when the index was much higher.

TABLE IV.

No.	Icterus index.	Dif. count.		Trans. per cent.	White.	Red.	Hb. per cent.	Stool.	Roentgen-ray diagnosis, probable.	Diagnosis.
		Polys. per cent.	Lymph. per cent.							
1	(7–17)* 13.0 (7–26) †9.0	65	27	7	9,800	4,270,000	80	Ameba histolytica	Pathological gall bladder	Chronic cholecystitis; chronic enterocolitis; acute bronchitis.
2	(–9)15* (7–13)6.2†	74	26	..	10,000	4,600,000	88	Negative	Duodenal ulcer; pathological gall bladder	Duodenal ulcer; chronic cholecystitis; chronic cholelithiasis.
3	13.5	50	43	4	5,600	4,290,000	82	Ameba histolytica	Pathological gall bladder	Chronic cholecystitis; chronic enterocolitis.
4	18.0	65	32	3	8,500	4,250,000	85	Negative	Pathological gall bladder	Chronic cholecystitis.
5	37.5	65	29	6	7,000	3,610,000	70	Negative	Pathological gall bladder	Acute cholecystitis.
6	15.0	66	32	2	6,200	4,160,000	80	Negative	Pathological gall bladder	Chronic cholecystitis; chronic arthritis; chronic enterocolitis.
11	12.0	84	16	..	13,600	4,160,000	80	Ameba histolytica	.....	Chronic cholecystitis; chronic enterocolitis.
12	10.0	69	29	2	8,800	2,210,000	30	Trichomonas	Pathological gall bladder	Chronic cholecystitis; chronic enterocolitis, chronic myocarditis.
13	20.0 28.3 15.0†	78	16	6	8,200	3,460,000	70	{Tenia saginata	.....	Tenia saginata; chronic enterocolitis; chronic cholecystitis.
14	20.0	58	42	..	7,000	3,210,000	68	Giardia, chilomastix	Pathological gall bladder	Chronic cholecystitis; chronic enterocolitis.
15	8.8	73	27	..	9,700	4,048,000	70	Ameba	Gall stones	Chronic cholecystitis; chronic cholelithiasis, chronic enterocolitis.
16	7.5	62	35	3	8,000	4,180,000	80	Negative	Duodenal ulcer; pathological gall bladder	Chronic cholecystitis; duodenal ulcer.
17	45.0	58	37	5	7,500	3,912,000	80	Ameba	Pathological gall bladder	Catarrhal jaundice; chronic enterocolitis.
18	18.0	65	29	6	7,500	4,650,000	78	Chilomastix	Gall bladder	Chronic cholecystitis; enterocolitis.
20	100.0	75	25	..	12,000	3,210,000	60	Negative	.....	Acute catarrhal jaundice.
21	20.0	70	30	..	8,600	3,920,000	70	Negative	.....	Chronic cholecystitis; rheumatic fever.
22	10.0	66	29	5	8,800	4,410,000	85	Negative	Pathological gall bladder otherwise negative	Chronic cholecystitis; chronic arthritis.

TABLE IV.—(*Continued.*)

No.	Icterus index.	Dif. count.		Trans. per cent.	White.	Red.	Hb. per cent.	Stool.	Roentgen-ray diagnosis, probable.	Diagnosis.
		Polys. per cent	Lymph. per cent.							
23	20.0	70	25	5	7,000	3,160,000	55	Negative	Positive for gall bladder; shadow	Chronic cholecystitis; chronic enterocolitis.
24	22.0	71	27	2	7,000	3,880,000	68	Ameba histolytica	Positive for gall bladder; shadow	Chronic cholecystitis; chronic enterocolitis.
25	24.0 6.0	68	32	..	7,800	4,250,000	75	Ameba	Negative for gall bladder; colon stasis	Chronic cholecystitis; chronic enterocolitis.
26	18.0	61	37	2	8,200	4,280,000	82	Negative	.....	
27	14.0	66	30	4	7,800	4,580,000	90	Craig	.....	Chronic cholecystitis; chronic appendix.
29	19.0	72	26	2	12,000	5,020,000	90	Negative		
30	15.0	79	18	3	5,400	3,580,000	70	Ameba histolytica	Duodenal ulcer; pathological gall bladder	Chronic cholecystitis; chronic enterocolitis; duodenal ulcer.
32	6.6	60	35	5	9,000	4,410,000	83	Ameba histolytica; trich. chilomastix	.....	Chronic enterocolitis.
33	6.6	56	38	6	7,600	4,210,000	85	Chilomastix	.....	Chronic enterocolitis.
34	5.4	72	25	3	9,400	4,948,000	80	Ameba	.....	Chronic enterocolitis.
35	6.0	87	13	..	16,000	4,470,000	77	Ameba	.....	Chronic enterocolitis; acute bronchitis.
36	5.7	61	36	3	7,800	4,120,000	80	Ameba	.....	Chronic enterocolitis.
37	4.2	62	35	3	6,900	3,544,000	70	Ameba	.....	Chronic enterocolitis; epilepsy.
38	7.5* 5.1†	70	29	1	10,400	4,320,000	85	Negative	Pathological gall bladder: colon stasis	Chronic enterocolitis; hernia from appendectomy.
39	6.6	..	..	..	14,800	3,920,000	..	Ameba	.....	Acute bronchitis; chronic enterocolitis.
40	7.0	77	23	..	16,800	4,290,000	90	Trichomonas	.....	Chronic enterocolitis; acute pleurisy.
41	5.0	58	42	..	7,500	4,250,000	75	Negative	Negative for gall bladder	Chronic enterocolitis.
42	8.0	64	35	1	5,600	4,620,000	92	Ameba	Negative for gall bladder	Chronic enterocolitis.
43	6.0	62	34	4	8,256	4,250,000	80	Ameba	.....	Chronic enterocolitis.
44	7.0	50	47	3	7,100	4,520,000	75	Negative	Duodenal ulcer; colon stasis; no gall bladder	Duodenal ulcer; colon stasis.
45	8.4	59	27	2	6,200	3,990,000	75	Ameba	Duodenal ulcer; chronic enterocolitis	Duodenal ulcer; chronic enterocolitis.

46	9.4	64	31	2	6,600	4,680,000	70	Negative	Duodenal ulcer; no gall bladder	Duodenal ulcer.
48	7.0	72	28	..	7,100	4,864,000	80	Ameba	Myocarditis	Chronic myocarditis, duodenal ulcer, chronic enterocolitis.
50	4.2	73	26	1	9,200	5,904,000	65	Ameba	Gastric ulcer; no gall bladder; colon stasis	Gastric ulcer; colon stasis; chronic enterocolitis; acute bronchitis.
51	4.4	82	15	3	13,600	3,190,000	56	Chilomastix	Gastric ulcer; no gall bladder	Gastric ulcer, varicose ulcer chronic enterocolitis; chronic nephritis.
54	19.8* 18.5†	63	37	..	6,600	5,088,000	65	Negative	Myocarditis, mass in hepatic region possible; cancer; fluid right chest	Cardiac failure, hydrothorax; general anasarca, malignant of liver.
55	10.0	..	..	..	10,200	5,920,000	..	Trichomonas	Myocarditis	Cardiac failure; chronic enterocolitis, hypertension.
58	4.0	74	25	..	6,300	4,432,000	75	Chilomastix	Negative except joints	Chronic arthritis; chronic enterocolitis.
59	3.4	67	33	..	9,900	5,848,000	85	Chilomastix	Negative except joints	Chronic arthritis; chronic enterocolitis.
60	7.5	60	38	2	5,500	4,144,000	80	Ameba histolytica	.....	Chronic arthritis; chronic enterocolitis.
61	6.2	62	38	..	4,500	4,520,000	75	Ameba histolytica	.....	Chronic arthritis; chronic enterocolitis.
62	6.6	60	38	2	7,600	4,064,000	85	Giardia cysts	Chronic appendix, negative gall bladder; colitis	Chronic arthritis; chronic appendix; chronic enterocolitis.
64	5.0	66	34	..	5,400	4,736,000	85	Chilomastix	.....	Chronic arthritis; chronic enterocolitis.
69	4.8	..	..	..	....	.....	..	.....	Carcinoma bowel	Metastatic carcinoma bowel, secondary anemia.
70	5.4	88	12	..	12,400	2,632,000	..	Negative	.....	Broad ligament abscess general peritonitis, secondary anemia.
71	4.2	66	34	..	9,100	3,880,000	75	Negative	.....	Syphilis, pyelitis.
72	8.2	59	41	..	8,300	4,262,000	80	Ameba	Kidney stone	Chronic enterocolitis, kidney stone, renal colic.
74	19.0	58	42	..	4,400	1,904,000	..	Ameba	Negative for gall bladder and kidney stone	Pernicious anemia, chronic enterocolitis.
75	9.4	66	34	..	4,900	1,472,000	..	Trich. chilomastix	Arthritis, malignant liver	Pernicious anemia, chronic enterocolitis, chronic arthritis.
76	9.0	67	33	..	3,600	2,022,000	60	Negative	Apical abscess, colitis, mass in liver	Pernicious anemia, apical abscess, chronic enterocolitis.
77	5.6	84	14	2	16,400	3,200,000	70	Negative	.....	Diabetic gangrene, chronic interstitial nephritis.

No. 71, Wassermann postive 4+.

* Index taken during attack.

† Index taken after attack.

Conclusion. We feel that this test is a valuable aid in differential diagnosis where there is pathology influencing the function of the liver. It is certainly highest in biliary diseases. The index returns to normal after such pathology has been removed. Gall stones that show no evidence of obstruction or active inflammation do not influence the index. Adhesions about the duodenum or gall bladder may by the blocking of ducts cause a rise in the index. Here the index may be an aid in differentiation between gastric and duodenal ulcer.

The uncomplicated secondary anemia show a hypobilirubinemia. This test helps to explain the presence of the Diazo reaction in the urine of typhoid patients, and by this fact it becomes much more diagnostic in this disease. With the Widal hemoclastic test it becomes measurably prognostic and aids in treatment.

The leukopenia of typhoid, malaria, etc., may be a direct physiological influence of the hyperbilirubinemia.

In closing we desire to express our grateful appreciation to our technician, Miss Estella Campbell, and to our pathologists, Drs. Brem, Zeiler and Hammock, for their scientific and painstaking care in the laboratory preparation of this work.

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REVIEWS.

ANGINA PECTORIS. By SIR JAMES MACKENZIE, M.D., F.R.S., F.R.C.P., LL.D., F.R.C.P.I., Director, St. Andrew's Institute for Clinical Research, Consulting Physician to the London Hospital and to H. M. the King in Scotland. Pp. 253; 77 illustrations. London: Henry Frowde, Hodder & Stoughton, Oxford Medical Publications, 1923.

MACKENZIE'S death before it was possible to write for this journal a review of his latest book, which only reached us in January, demonstrates how actively he was employed to the very end. Though this is not the place to expatiate on the virtues of this eminent cardiologist, the reviewer cannot refrain from lamenting this great loss to medical science, at the same time expressing appreciation of the forethought which founded the St. Andrew's Institute for Clinical Research, and thus ensured that his good works would continue after him.

Books from Mackenzie's pen have always been interesting and useful because one could be confident that the statements were the author's own and not borrowed from others and that they had the valuable background of long experience as well as a very original mind. The present volume is no exception to the rule and constitutes a valuable addition to the study of angina pectoris. Nevertheless, the very defects of the author's virtues make it necessary for the reader to beware of accepting as settled many of the dogmatic statements about subjects which are still open questions; and for him to remember that much valuable evidence from other sources is not only not mentioned but apparently had not even been known to the author.

Assuming thirty years ago from the divergence of opinion on the subject of angina that the method of inquiry was defective, Mackenzie started from the new point of view of investigating pain, as the most prominent feature of the condition. This naturally led him to inquire what were the structures concerned, what kind of stimulus was adequate to produce the pain, how it was conveyed to the sensorium, what conditions led to its production and what effect it had on the patient's life. This in turn led him back to the underlying question of heart failure, where he was so impressed with the "woefully defective" state of our knowledge that he laments "that no real advance can be made in our knowledge of

angina pectoris, or, indeed, in any matters concerned with the heart" clinically, until the matter is remedied. (This from one who has added so much to our knowledge of the mechanism of the heart beat and heart failure is significant and characteristic.)

Nevertheless in the present book he developed these ideas, which led him to formulate his now well-known view that the pain of true angina is due to heart muscle contraction in the absence of sufficient blood supply—usually occurring, to be sure, as a result of coronary disease, but possibly also from a direct exhaustion or degeneration of the heart muscle with normal coronaries. The heart pain noticeable to a hypersensitive nervous system, he labels secondary angina pectoris (in other words, the older "pseudo-angina") and here does not consider the heart primarily at fault. In order to explain the production of the pain, the theory of disturbed reflexes —enthusiastically pursued but not really invented at the St. Andrew's Institute—is invoked, the exhausted muscle supplies the stimulus, which is felt as pain in the appropriate referred zone, the stronger the stimulus the larger being the zone affected.

On this basis an interesting, stimulating and instructive structure is reared, which will be of permanent value to students of the subject. The appendix of almost 100 pages with records of 160 cases is one of the most valuable features. The easy style, fundamental method of treatment and pleasant make-up of the book add to its readability. E. K.

THE THEORY OF DECREMENTLESS CONDUCTION IN NARCOTIZED REGION OF NERVE. By GENICHI KATO, Professor of Physiology, Director of Physiological Institute, Keio University, Tokyo, Japan. Pp. 166; 126 figures and tables. Nankodo, Hongo, Tokyo, Japan, 1924.

PROFESSOR KATO'S experiments disprove the hitherto accepted notion that in traversing a partially and uniformly narcotized region the nerve impulse undergoes progressive decrease in intensity. Instead, the impulse, though subnormal, is constant throughout the region. Through a series of careful tests, the sources of error in the previous evidence are made clear. One of these tests incidentally offers a new line of evidence for the all-or-none law in nerve, in place of Adrian's previous apparent proofs, now rendered invalid by Kato's disproof of decremental conduction. Moreover, the all-or-none law is shown to hold also in narcotized nerve—thus our notions of nerve conduction are helpfully unified. The implications of this work as to the properties of the synapse are not as revolutionary as might be supposed—for example, the facts of Wedensky inhibition, not treated by Kato, remain, though they need some reinterpretation.

Some minor shortcomings of method and proof are to be condoned in view of the magnitude and clear-cut result of the work as a whole, which should prove a great stimulus to the advance of nerve physiology. D. B.

A Textbook of Vertebrate Embryology Treated from the Comparative Standpoint. By Ruth L. Phillips, Ph.D., Professor of Biology, The Western College for Women, Oxford, Ohio. Pp. 302; 137 illustrations. Price $3.50. Philadelphia, and New York: Lea & Febiger, 1925.

This compact little book, clearly and accurately written and well got up by the publisher, should be of value to biologists needing embryological information, as well as to the students for whom it was designed. Though "written with the idea of furnishing a short, concise test to supplement the all-important work of the laboratory," it should frequently be useful in obviating longer search in the more exhaustive textbooks of the subject, many of which are rather hopelessly out of date. Following a short historical sketch, are four chapters on cell development through the embryonal membrane stage, with a second part of seven chapters on organogeny.

E. K.

Materia Medica for Nurses. By A. L. Muirhead, M.D., Late Professor of Pharmacology, Creighton Medical College, Omaha, Nebraska and Edith P. Brodie, A.B., R.N., Washington University School of Nursing, St. Louis, Missouri. Second edition. Pp. 190; 25 illustrations. St. Louis: The C. B. Mosby Company, 1924. Price $2.00.

The purpose in revising this book seems to have been to reclassify the drugs according to their action on the various systems, to include in the discussion a brief review of the physiology of the system and to add new sections on the preparation of solutions and dosage. About one-fourth of the entire book is devoted to material usually covered in the course in drugs and solutions. The text is concise, readable and accurate. The chief criticism is the brevity and elementary character of the material. However, the authors state it has been their aim to provide the student with an adequate working knowledge of the subject "in the simplest and briefest form and at the same time to meet as satisfactorily as possible the recommendations for instruction in Materia Medica outlined in Standard Curriculum for Schools of Nursing." This book would need to be supplemented by additional material to fulfill the latter function. S. G.

SURGICAL PATHOLOGY. By WILLIAM BOYD, M.D., M.R.C.P. (ED.), F.R.S.C., Professor of Pathology, University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Pp. 837; 349 illustrations and 13 colored plates. Philadelphia and London: W. B. Saunders Company, 1925. Cloth, $10.00 net.

THE appearance of two new large books on Surgical Pathology within a twelve-month inevitably invites a comparison between them. While books of the caliber of McFarland's and Boyd's would in any case be welcome additions to a subject which has hitherto been but poorly represented in the medical literature of the English speaking world, they are especially so in that they approach the subject from somewhat different points of view (both mental and geographical) and to that degree are complementary. As compared with McFarland's work (see review in AM. JOUR. MED. SCI., 1924, **168**, 603), Boyd has dealt with the subject matter in a more systematic and inclusive manner, thus offering a greater chance that the query of the person seeking information will be answered, even though that answer may be less original and forceful. Even the illustrations are cases in point, being not infrequently borrowed from other sources, but of such appropriateness and excellence that they correspondingly improve the ensemble of the book.

The first quarter of the book is devoted to twelve chapters on General Pathology, on such subjects as bacteriology, inflammation, healing, tuberculosis, syphilis, shock, tumors. In the remaining three-quarters—twenty-five chapters on Special Pathology—special systems, individual organs and single diseases are discussed. A chapter on nerve pathology is conspicuous by its absence, though a few nerve tumors are treated in the first section.

In a short foreword, Dr. W. J. Mayo points out that Dr. Boyd has tried to produce "a work that will serve as a handbook to the surgeon, and the internist, and a guide to the beginner in the (this?) field of medicine." For this reason perhaps the very elementary treatment of the chapter on bacteriology may be justified; otherwise it would seem that the cursory descriptions of the common organisms mentioned might better have been either amplified or omitted. There is even less justification for calling the pneumococcus a small oval coccus, or to speak on one page of the "failure of the Gram-positive and acid-fast bacteria to stimulate the body to an immunity response" and on the next to assert that "it is in staphylococcal infections of the skin that some of the most gratifying results of vaccine therapy have been obtained."

The book is admittedly "didactic in tone, as is necessary in a volume of this scope, not judicial, fortunately, because to be judicial one must deal only with proved facts and give no play to scientific imagination." Leaving aside the objection naturally to be made to the latter statement, one can emphasize that here, as in most

medical works, didactic treatment calls for a corresponding reserve of acceptance on the part of the intelligent reader. Exception might be taken also to the implied slight in the Foreword to the value of the postmortem room and the "cadaverization" of biopsy specimens, if by this phrase is meant the examination of biopsy specimens in paraffine as well as in frozen sections. Broader and more logical is the opinion of the author who, fully unholding the value of Moynihan's "pathology of the living" and the advances that it has caused, nevertheless still recognizes that "the fundamentals of pathology must be learned in the postmortem room," where the disease process, end-results though it may be, "can be seen as a whole, and the clinical picture viewed in a way that will often make light the dark places of the case."

To the actual treatment of his subjects, the author has brought an easy style and a philosophical, historical flavor that pleasantly illuminate the results of his extensive study of the works of others, and his considerable personal experience. The influence of the best modern leaders in pathology and of the medical experiences of the war can be read in and between many lines.

"References for further study" at the end of each chapter are purposely made brief "to induce the reader to go further afield in his search for knowledge." To the reviewer, it would seem more appropriate to lengthen these lists, even at the risk of "seeming to display the erudition of the writer," in order to aid the reader in going much further afield. Inducement should not be necessary to those most worth catering to.

As is usual with Saunders books, the make-up leaves little to be desired; the paper is good, the type pleasing and well placed, the index adequate, the illustrations attractive and true to life and yet demonstrate what they are supposed to demonstrate. All in all the book well fulfills its object "to present those aspects of pathology which will prove useful to the surgeon" and should be of value to the pathologist as well. E. K.

HUMAN CONSTITUTION. By GEORGE DRAPER, M.D., Associate in Medicine at Columbia University, New York City. Pp. 345; 208 illustrations. Philadelphia and London: W. B. Saunders Company, 1924.

THIS book is written for the purpose of outlining a uniform scheme whereby physicians interested in the human body might have a model upon which to base their observations. No attempt, says the author in his preface, is to be made to develop a method of diagnosis, "although obviously in the train of a study of constitution aids to diagnosis will appear." Following out this declared intention, the book is divided into seven chapters; the first few deal with

the general principles of anthropological measurements, order of examination, methods of examination and analyses of the curves. A very long chapter now follows discussing many charts and containing the kernel of Dr. Draper's researches. In this chapter, the variations that occur in the measurement of different individuals suffering from six diseases—gall bladder, peptic ulcer, nephritis, pernicious anemia, tuberculosis and asthma—are verbally discussed and graphically illustrated. They are interesting and instructive and yet one would be rather inclined to look with a certain skepticism upon deductions that are drawn from such a few cases; for example, gall bladder disease, 17 cases; pernicious anemia, 21 cases and so on, in spite of the preficatory defense of the method "of combining accumulative percentage curves and relative frequency curves . . . by means of which, with a smaller number of observations than have heretofore been acceptable, significant differences can be readily interpreted." A further criticism might be added: The art of measuration is a difficult one and probably few clinicians would be willing to devote the time and the care, nor would they have the ability to make such exact and minute measurements as are apparently required.

An objection or two to this work has been cited. Yet Draper has done a real service to medicine in attempting to put upon a scientific basis the study of anthropometry. It was not so many years ago that the clinician was speaking familiarly but in the most general terms of the lymphatic habitus, the apoplectic, the enteroptotic or the phthisical; but it has remained for the author of this little book to study scientifically the so-called habitus of the patient. In 1761 Auenbrugger wrote upon immediate percussion, a great discovery which remained unnoticed until Corvisart, in 1808, brought it again before the eyes of the medical world. Perchance Draper will be the Corvisart who will show generations to come that anthropometry is an invaluable aid to diagnosis.

J. M.

A Manual of Psychiatry. By Paul E. Bowers, M.S., M.D., Lecturer in Neuropsychiatry, Post-Graduate Medical School of the University of California. Pp. 365. Philadelphia and London: W. B. Saunders Company.

Briefly and clearly, the accepted views regarding mental diseases are here set forth, controversial material being eliminated. The compact form, and systematic method of treatment will commend this work to the student or practitioner who desires a readable and reliable handbook of Psychiatry. J. A.

OPERATIVE SURGERY. Covering the Operative Technic Involved in the Operations of General and Special Surgery. By WARREN STONE BICKHAM, M.D., F.A.C.S., Former Surgeon in Charge of General Surgery, Manhattan State Hospital, New York; Former Visiting Surgeon to Charity and to Touro Hospitals, New Orleans. In 6 octavo volumes totalling approximately 5400 pages with 6378 illustrations, mostly original and separate Desk Index Volume. Volume VI, completing the set, contains, 989 pages with 1224 illustrations. Price $60.00. Philadelphia and London: W. B. Saunders, Company, 1924.

BICKHAM'S Operative Surgery is now complete with the appearance of the sixth volume and index. This volume maintains the standard set by its predecessors. It deals chiefly with Neurological, Gynecological and Orthopedic Surgery. The latter is only a sketchy summary. It could hardly be used as a satisfactory guide for work in this field. The remainder of the book is the usual compilation of recognized operations well described and pictured. Considerable maturity of surgical judgment is required in the employment of a work of this kind owing to the necessity for selection of the operation to fit the case. This is, however, not a criticism. As a thesaurus of operative methods it is invaluable. The index is well done and adds greatly to the utility.

D. P.

MONOGRAPHS ON SYSTEMATIC BACTERIOLOGY, VOLUME I, GENERAL SYSTEMATIC BACTERIOLOGY. By R. E. BUCHANAN, PH.D., Professor of Bacteriology, Bacteriologist of the Iowa Agricultural Experiment Station and Dean of the Graduate College, Iowa State College, Ames, Iowa. Pp. 597. Baltimore: Williams & Wilkins Company, 1925.

THIS volume represents the first of a series of monographs prepared under the sponsorship of the Society of American Bacteriologists dealing with the general field of systematic bacteriology. The first chapter deals with the history of the various classifications of bacteria which have been proposed up to the present time, bringing together much material from widely scattered sources which have been for the most part difficult of access. In the second chapter codes of nomenclature are presented, while the third and final chapter presents an alphabetical list of the names used by various authors to designate bacterial subgenera, genera, and higher groups compiled from a comprehensive study of the literature. An extensive bibliography is appended.

J. S.

THE PRACTICE OF PEDIATRICS. By CHARLES GILMORE KERLEY, M.D., Attending Physician, to the New York Nursery and Child's Hospital, and GAYLORD WILLIS GRAVES, M.D., Associate in Diseases of Children in the College of Physicians and Surgeons (Columbia University). Third edition. Pp. 922; 150 illustrations. Philadelphia and London: W. B. Saunders Company.

THE third edition of this standard work on pediatrics contains much that is new, and much of the text of the previous edition has been rewritten. The recent advances in our knowledge concerning scarlet fever, diphtheria, diabetes, rickets and many other diseases will be found included in these pages, while many of the older articles and illustrations have been omitted. As a clear and authoritative textbook on pediatrics this edition will appeal even more than its predecessors to the general practitioner, pediatrician, and medical student. J. A.

PRACTICAL SURGERY ILLUSTRATED. By VICTOR PAUCHET. Translated by F. R. B. ATKINSON, Volumes I and II, pp. 545; 416 illustrations. London: Ernest Benn Limited, 1924.

THIS unique work carries with it unusual interest in view of the fact that it is the product and the representation of one man's activities. He describes and illustrates in a most profuse fashion actual operations performed by the author and other French surgeons. All of the illustrations are absolutely new; in fact, have been created at the time of that particular operation. They are large, some of them being full-page size which is an advantage in that a greater amount of minutiæ and detail can be portrayed. The text itself takes a minor place when the value of this work is considered. In fact, the text constitutes but a very small proportion of the page space in these volumes. Its one idea is to describe the illustrations. The books as volumes are distinct and each one sufficient unto itself. It can in no way be considered a system of surgery but, however, fills a most important place in the surgical armamentarium of today. It is a good, comprehensive and clearly presented operative surgery. E. E.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Skin Infection of Rabbits with Hemolytic Streptococci Isolated from a Patient with Erysipelas.—T. M. RIVERS (*Jour. Exper. Med.*, 1925, 41, 179) describes a method of demonstrating protective action of immune sera with an organism which he isolated from a human case of erysipelas and which culturally and morphologically resembles hemolytic streptococci. He first shows that cultures of this organism when injected intracutaneously into the shaved abdomen of the rabbi , produced nine times out of ten large severe abscesses. In the tenth case a lesion would be produced which was characterized by redness and swelling of the skin outside the phlegmonous area, extending in all directions, the advancing margin being irregular and slightly red. The lesion would continue to spread for six to seven days and then subside. This was followed by a marked desquamation of the involved skin. This lesion, as described above, appears to be truly characteristic of the lesion that is seen in cases of human erysipelas. The next step in this study was the production of an immune serum by injecting intracutaneously 0.2 cc of a suspension of the streptococci, making in all 7 injections, seven days apart. Eight days after the last injection the animals were bled and their sera pooled. The immune serum was then mixed with varying dilutions of the streptococci and injected intradermally. For controls, equivalent mixtures of normal sera and streptococci were employed. The control areas were all characterized by the formation of large nodules filled with pus and covered with scabs. The areas inoculated with the immune serum mixture showed little change from the normal skin. Should this method of demonstrating the

immune properties of antistreptococcic serum prove of general applicability, Rivers writes that it will possess a number of advantages which are absent from the ordinary methods of testing for protective action of sera. It may be not only a method of testing the potency of sera for therapeutic purposes, but also a method of testing the specificity of different strains of the streptococcus.

Local Passive Immunity in the Skin of Rabbits to Infection with (1) a Filterable Virus, and (2) Hemolytic Streptococci.—In another communication on somewhat the same general lines as the one abstracted above, RIVERS (*Jour. Exper. Med.*, 1925, **41**, 185) shows that when small areas of skin are infiltrated with normal serum of meat broth these areas are more refractory than normal skin to infection with hemolytic streptococci, a nonspecific reaction which is, however greatly intensified if a homologous immune serum is employed. The author very pertinently suggests that in erysipelas it might be possible to prevent the spread of the infection by injecting at the margins of the healthy skin immune serum which would make it refractory and prevent further spread of the infection.

Contributions to the Pathology of Experimental Virus Encephalitis. I. An Exotic Strain of Encephalitogenic Virus.—S. FLEXNER and H. L. AMOSS (*Jour. Exper. Med.*, 1925, **41**, 215) during the course of an extensive research upon the etiology of epidemic encephalitis, in which 100 specimens of cerebrospinal fluid were injected into rabbits, obtained an exotic virus from the fluid of an individual suffering from cerebrospinal lues who at no time had symptoms other than those referable to his syphilitic infection. This was the only virus which was capable of producing an inoculable disease and it was found in only one of three different specimens of the cerebrospinal fluid obtained from the same source. The finding of this exotic virus, the J. B. virus, apparently serves "to clarify the obscurity and confusion now enveloping the so-called virus of encephalitis." This virus, as is shown by the authors, differs biologically in no way from the virus of herpes and encephalitis. It is apparently a herpes virus which has entered the cerebrospinal fluid and, if such is the case, it shows that the virus obtained by others is probably merely another instance of the ubiquitous herpes virus entering the spinal fluid and discovered by chance. The J. B. virus possesses a strong affinity for the brain structures of the rabbit, but as it was isolated from a patient presenting none of the symptoms of epidemic encephalitis, it seems highly probable that the herpetic virus has a different action on the brains of the two species, man and rabbit. There is no warrant for ascribing epidemic encephalitis in man to a virus which is apparently merely a type of herpetic virus solely because it produces marked cranial disorders in rabbits. To the experimental disease produced in rabbits by the inoculation of the herpes and allied viruses, Flexner and Amoss propose the name Virus encephalitis.

SURGERY

UNDER THE CHARGE OF

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Intravenous Continuous-drop Infusion.—EICK (*Centralbl. f. Chir.*, 1924, **47**, 2575) describes simple apparatus and refined technic for this procedure. The author uses routinely a trade preparation called Calorose, a mixture of equal parts of dextrose and levulose. Figures are cited of 18 cases saved by this procedure in a series of 82 moribund patients. The author, however, feels that the procedure as a routine after operations has distinct merit, especially in long continued operations with loss of much blood. In cases of ileus, peritonitis or uremia, good results have been reported. The procedure is contraindicated in heart, lung, and kidney disorders.

Roentgenologic Diagnosis of Cholecystic Disease with the Aid of the Sodium Salt of Tetrabromphenolphthalein.—CARMAN and COUNSELLOR (*Am. Jour. Roentgenol.*, 1924, **12**, 403) state that the dye should not be used in cases where obstruction was known to exist. The typical severe reaction is one of vasomotor shock. It usually begins within five to ten minutes. Normally the gall-bladder will retain sufficient dye to cast a shadow at the fourth or fifth hour after administration. This shadow attains its greatest intensity sometime between the eighth and twenty-fourth hours. It becomes thinner thereafter and should disappear between the twenty-fourth and forty-eighth hours. The shadow is oval or pyriform with an even contour and should be homogeneous. It is larger at earlier than at succeeding hours. This variation in size is important evidence of normal distensibility and contractability. Abnormal responses include failure of the gall bladder to fill with the dye, scanty filling as shown by persistent faintness of the shadow, delayed filling, marked delay of emptying, deformity of contour, unvarying size of shadow, constant extremes of size and mottling or central defects. In the absence of cirrhosis or gross impairment of hepatic function, interference with filling suggests obstruction due to gall stones, adhesions, new growths, thickened bile or other pathological conditions. Unvarying size of the shadow implies loss of elasticity of the gall bladder walls. Mottling of the shadow suggests stones or papillomas.

Splenectomy in Egyptian Splenomegaly.—COLEMAN and BATEMAN (*Lancet.* 1924, 1116) state that splenectomy has been advised in all suitable cases since 1920. Probably 50 per cent of those seen in outpatient departments are refused operation at once, owing to definite

contraindications, considerable ascites, pellagra, disease of the heart, and advanced general debility. The remainder are advised admission for observation and further examination and the majority agree to this. Most are suffering from ankylostomiasis and bilharziasis, either rectal or urinary and these diseases are treated before the blood is examined. Preliminary treatment takes two or three weeks, as a rule. The authors have learned from experience to know beforehand from the shape of the spleen, which are difficult cases. A spleen very long from above downward means a long pedicle, and can be tackled piece by piece. But a broad spleen extending medially beyond the midline means a thick, bunched-up pedicle in which the vessels are difficult to reach and secure individually. The spleens removed have varied from $1\frac{1}{4}$ pounds to $12\frac{1}{2}$ pounds. The average for the series is $3\frac{3}{4}$ pounds. The mortality is still high, but untreated cases so easily develop extreme ascites that the operation is justifiable.

The Sacro-iliac Joint: Its Diagnosis as Determined by the Roentgen-ray.—DARLING (*Radiology*, 1924, **3**, 486) says that backache has more to do with the soft tissues, ligaments, muscle fibers, bundles and sheaths, nerves and neuralgia than dislocations of joints. Sprains, sacro-iliac and lumbosacral, séem more likely than demonstrable relaxations or subluxations. The sacro-iliac joint has a synovial lining and is, therefore, subject to arthritis, due to any focus of infection. Sacro-iliac strain, relaxation, subluxation or dislocation may exist clinically, but cannot be shown definitely by the roentgen-ray examination if and where the motion consists of a forward and backward tilting of the sacrum, in relation to the ilium. Where there is actual separation of the pelvic girdle, such as complete fracture with displacement or a complete separation at the symphysis, then only will there be shown by roentgen-ray a definite sacro-iliac separation relaxation. Radiographs made improperly are often misinterpreted as showing separations, which do not exist. This is a too common error, due to zealous attempts to make or support a diagnosis.

Necrosis of the Kidney.—FALCI (*Jour. d'Urol.*, 1924, **18**, 449) declare that total destruction of the kidney from renal infarct follows a definite infection of the cardiovascular type as a general rule. Cases following specific diseases, such as diphtheria or scarlet fever, are extremely rare. The symptoms and signs are not definite to a pathognomic degree. Onset is rapid, course violent, while pain has its location in the renal area. The urinary findings are significant. Diagnosis, while difficult, is essentially possible, especially if the previous medical history and cardiovascular findings are weighed judiciously. The prognosis is exceedingly grave, 86 deaths in 100 collected cases. Nephrectomy is the treatment in unilateral necrosis of the kidney.

Ideal Prostatectomy.—BURK (*Centralbl. f. Chir.*, 1925, **52**, 113) states that the primary closure of the prostate bed and the wound in the bladder makes a great advance in the field of prostatic surgery. Merten of Bremen has brought forward this method with report of follow-up studies, upon his cases. The advantages of the method lie in prevention of infection in the space of Retzius and in the layers of abdominal

wall, factors which have destroyed the lives of aged, weakened patients. Other favorable features of this procedure are the reduction in time of illness and the severity of the illness. Secondary hemorrhage from the prostatic bed is the cardinal danger in this method, as described by Merten. The present author does not feel that the simple suturing of the mucous membrane in the base of the bladder is sufficiently safe, for the bleeding is usually marked enough to prevent extremely accurate suturing. He then describes an evolved technic for bringing the prostatic bed well into view and under excellent control by rectal instrumentation. He reports the after course of several cases.

Operation upon Recent Patellar Fractures with Sutures of Fascia Lata.—VORSCHÜTZ (*Centralbl. f. Chir.*, 1925, **52**, 179) says that treatment has become essentially operative. The series of operative cases collected by Thiem showed a mortality of 10 per cent, while unoperated series showed a mortality of 3 per cent. He discusses the merits of the encircling suture and the process of passing sutures through the fragments. He discusses the choice of suturing materials. He gives in detail the studies upon wiring and its after course. He shows that the fascia can give certain results that the wire cannot, for the fascia is not "foreign body" and therefore can be incorporated in the organic processes of the body. While the wire in the course of time, becomes attenuated and loosened by chemical processes and other forces, the fascia becomes firmer and tighter because it enters into the fibrous organization, holding the fragments more tightly as the process continues.

Abduction Treatment of Fracture of the Neck of the Femur.—WHITMAN (*Ann. Surg.*, 1925, **81**, 374) states that the results even in the cases treated for fracture, as distinct from those in which the saving of life has been the first consideration, have always been extraordinarily bad. Neglect of the fracture passed as consideration for the patient, functional disability as an inevitable consequence of the injury and nonunion as evidence of incapacity for repair. The inception of a radical reform dates from 1890, when the author identified a fracture of the neck of the femur in a young child and reported it as a surgical curiosity. The incomplete or impacted fracture caused disability, not because of direct shortening, but because the deformity checked the range of abduction and induced an accommodative distortion of the limb. Nonunion in childhood could not be explained by insufficient nutrition, but was evidently the result of separation of the fragments. It was equally evident that conventional methods were inadequate either to correct the resistant deformity of the incomplete fracture, or to oppose displaced fragments securely. The author compares the series of Campbell with that of Smith, and early Victorian authority, whose mortality was 63 per cent. He makes this graphic contrast because the conventional practice has not materially changed in the interval and because it is still generally assumed that efficient treatment of the fracture is more dangerous than life-saving neglect. The abduction treatment is rarely described in practical detail in textbooks and either by inadvertence or intention, various modifications have been introduced, none of which appears to offer any advantage over the original but quite the contrary.

PEDIATRICS

UNDER THE CHARGE OF

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Energy Metabolism of Normal Newborn Babies, with Special Reference to the Influence of Food and of Crying.—MURLIN, CONKLIN and MARSH (*Am. Jour. Dis. Child.*, 1925, **29**, 1) describe some improvements in the respiration apparatus designed to make measurements of oxygen absorption more accurate. The maximum error in the measurement of oxygen, and therefore on the heat production, is approximately 5 per cent. Two hundred and thirty-four observation periods on 50 newborn infants, ranging in age from six hours to fifteen days, are recorded. Of this number only ninety-eight periods with 38 infants may be described as truly basal, where the infant slept quietly throughout. The basal metabolism for these 38 infants averaged 6.67 calories per hour, or 2 calories per kilogram and 29.16 calories per square meter per hour. The respiratory quotient in these basal periods ranges from 0.66 to 1.16. The average of all quotients whether basal or not was from 0.79 the first twenty-four hours to 0.75 on the fourth day and then gradually upward to 0.85 on the ninth day. The basal heat production was highest in the second twenty-four hours. From this point it fell gradually and uniformly on the basis of surface to the sixth day, from which point it rose steadily. Applying statistical methods, it was found that, lumping all observations together, there was practically no correlation between heat production and the pulse rate. With regards to the influence of crying on energy metabolism, the interesting observation was made that in the average normal infant active healthy crying required just as much expenditure of energy as the basal metabolism while asleep. Expressed differently, crying 1 per cent of the time raised the metabolism 1 per cent. Special attention was given to the effects of natural food and of supplementary feeding of lactose and dextrose solutions on the respiratory quotient and on the basal heat production. It was found particularly difficult to raise the respiratory quotient by means of single supplementary feedings on the second and third days. The respiratory quotient accurately determined may be taken as an index of the state of nutrition. If sufficient food is given to insure a respiratory quotient of 0.9 or above within two and a half hours after feeding the state of nutrition will be good and the child will be gaining weight. The dynamic action of ordinary feedings or of supplementary feedings within the first eight days is very small. The largest recorded was 12 per cent from a feeding of 10 per cent lactose. The same was found with dextrose. Comparing the effects of small feedings, averaging 26.7 gm., of food or of the sugar solutions with that of larger feedings, averaging 51 gm., the increase in the basal heat production, due to the addition of 24 gm. was approximately 7 per cent average.

Studies in Tuberculosis: The Significance of Lymphangitis Occurring with Cutaneous Tuberculin Tests in Children.—EBERSON (*Am. Jour. Dis. Child.*, 1925, **29**, 29) claims that the obvious deduction from his clinical and experimental study of tuberculin reactions and associated lymphangitis was that the phenomenon was specific and had some diagnostic as well as therapeutic significance. An interpretation of this observation presupposes a knowledge of facts which may have some bearing on the mechanism of a tubercle infection in relation to lymphatics and lymph glands. A search of the literature does not produce pertinent data regarding lymphangitis in relation to this phase of the problem. Conheim pointed out long ago that the tubercle bacillus leaves its mark on the lymph glands and the afferent trunks which drain the site of entry of the infection. Tubercle bacilli have been found to take a direct path to the proximal gland in their course along the lymphatics by means of phagocytic cells. In this process some organisms are destroyed, while those that are not give rise to a tuberculous focus in the lymph gland. The toxin which is produced by the bacilli causes lymphocytosis, which in turn serves to reduce the vulnerability of an adjacent gland as a result of a narrowing of the sinuses. It is not mere speculation to state that such a mechanism entails local as well as a more widespread sensitization, of which the phenomenon of lymphangitis appears to be an objective demonstration. It is of further interest in this connection to consider the question of what relation, if any, exists between the severity of a tuberculin reaction and the specific infection with tuberculosis. It would seem that there is some justification for stressing the value of correlated findings, such as a severe tuberculin reaction and the presence of the disease. The writer feels that the significance of lymphangitis with tuberculin reactions is to be considered from the standpoint of an infection with tuberculosis, which in children manifests itself as a glandular disease. The lymphatics are the distributors, and the phenomenon of lymphangitis speaks for an active tuberculous process. A glandular reaction following an injection of tuberculin is akin to a more pronounced skin reaction and is in turn an integral part of the most pronounced reaction, lymphangitis, which results from an active sensitization of the lymph channels to the products of the tubercle bacillus.

Serum Prophylaxis of Epidemic Parotitis.—REGAN (*Jour. Am. Med. Assn.*, 1925, **84**, 279) immunized six groups of children, comprising 81 in all, exposed to epidemic parotitis at different times. He used an average injection of 3 cc of convalescent serum within a period varying from the first to the sixth day after exposure. Only 1 of these patients developed mumps, but 11 were discharged from observation before their possible incubation period was over, and the results in these 11 immunized patients are not known. The remaining 69 showed no evidence of the disease. The convalescent blood used for their immunization was taken from healthy adult donors, who were Wassermann negative and clinically free from any active signs of tuberculosis. The blood was collected between the extremes of the tenth and the twentieth day, usually the fourteenth or sixteenth day of their disease. It should be administered before the seventh day after exposure to

afford complete immunity. The possible value of the method of modifying the disease by injecting the serum late in the incubation and in somewhat larger doses may be of some use, and this may prove particularly advantageous in the prevention of orchitis.

Studies of the Salivary-urea Index in Children.—CALVIN and ISAACS (*Am. Jour. Dis. Child.*, 1925, **29**, 70) determined the salivary-urea index in 196 children, the ages of whom ranged from two and a half to sixteen years. Eighty-five had normal urines; 111 had albuminurina, of which 10 had definite evidence of nephritis. Blood-urea determinations were made on 25 of these children, 3 of whom had normal urinary findings and 22 of whom had definite evidence of nephritis. The normal lower limit of the salivary-urea index in adults is 30. The salivary-urea index in this series generally averaged lower than the adult. The lowest index was 23, in a child of nine years. The highest was 50 and the average was 35. The age range apparently made little difference among the children studied, those above eight years averaging 35.8, and those below 8 averaging 34.8. Twenty-three of the total number of salivary indexes determined were below 30, and of these 13 patients had negative urines and 10 had some albuminuria. The lower trend of the figures in children corresponds to the generally accepted lower averages of normal blood urea, perhaps due to a lower protein intake. The relation of the level of the salivary-urea index to the protein content of the diet is being studied by the authors. The youngest child in this series was two and a half years of age. It was found too difficult to get the coöperation of younger children to complete the necessary chewing and expectoration. Several children were aged four years, and the oldest was sixteen years. Most of the children between three and six years coöperated readily, especially when the parent or nurse was near to watch the child and to encourage chewing and expectoration. Several children between the ages of three and eight years would not coöperate or were unable to understand what was wanted. In 2 cases in which coöperation was poor, and two hours elapsed before a sufficient quantity of saliva was collected, the salivary index was over 50, although the blood urea was normal. This can probably be accounted for by the autolytic changes in the saliva while standing. In 3 cases small amount of macroscopical blood from the gums was present in the saliva. This apparently did not change the index values, which varied from 36 to 48. In this series are included 111 children whose urine revealed albumin, varying from a trace to 4+; 99 with albumin from trace to 2+ and with no casts or occasional ones had a normal salivary-urea index; 2 others of this group had a high index, but had chewed for two hours as described above. Of the 10 children with definite marked nephritis, 4 had a normal salivary index, ranging from 34 to 38, and 6 showed a high index from 60 to 105, denoting urea retention, which was confirmed by blood-chemistry studies, the blood urea in the first 4 ranging from 15 to 24 mg., and in the last 6 from 58 to 110. The albuminurias of mild grade without evidence of serious kidney damage did not average any higher salivary index than did the normal cases. No patient showing a salivary-urea index below 50, on which a blood determination was done, showed a blood-urea value over the accepted

normal limit of 25 mg., and *vice versa;* the only children whose salivary index was over 50, and whose blood urea was normal, were the 2 who chewed for two hours, allowing autolysis to progress in the expectorated saliva. The 6 patients other than these 2, which had a high salivary-urea index over 50, had correspondingly high blood-urea values, and all were nephritics. The authors recommend the salivary-urea test in children because of the ease with which a specimen of saliva may be obtained.

Calcium and the Acid-alkali Balance.—HUMMEL (*Klin. Wchnschr.*, 1924, **3**, 2384) shows that rickets and spasmophilia, although belonging clinically to the same group, have an opposite tendency in metabolism, the rickets being acidotic and the spasmophilia being alkalotic. The common point is the change connected with calcification of the bones. Calcium carbonate can be deposited from the bicarbonate only in an alkaline reaction. This reaction of the medium disappears when the calcium carbonate has precipitated. Since the process is reversible, high degrees of alkalinity occur if the precipitation of calcium carbonate is prevented. Calcified bones give an alkaline reaction, while the osteoid tissue is acid, as long as it is unable to take up lime. The gravest cases of rickets are not spasmophilic, because there are so many acid proteins of the osteoid tissues that the hydroxyl ions are easily saturated. A spasmophilic condition with its alkalosis is already a step toward the cure of the rickets.

OBSTETRICS

UNDER THE CHARGE OF

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Intracranial Bleeding in the Newborn.—SAENGER (*Monatschr. f. Geburtsh. u. Gynäk.*, 1923, **65**, 257) contributes a paper upon this subject from the clinic in Munich. He finds that intracranial bleeding in the newborn is very common. In 100 autopsies in 73 cases macroscopic evidences of bleeding were present. Of these, 46 had severe hemorrhage. Considerable bleeding developing during birth penetrates the subdural space and makes the subdural fluid blood stained. One cannot accurately distinguish between supratentorial and infratentorial bleeding. The cause of this accident is found in the simultaneous action of interference with fetal circulation during labor and the direct application of force in the delivery. The anatomy of the circulation is such that hemorrhage is frequently found in the right cranial sinus, as this is a point where an interruption in the circulation cannot occur without injury to the tissues. When congestion or prolonged interruption develops there is increased tension in the vessels which is communicated to the duplications of the dura, especially those above and below the large sinus bordering on the tentorium cerebelli. Clinical observation shows

that contracted pelvis, very strong labor pains, rigid birth canal, thin cranial bones in premature children and especially large children, are factors tending to this injury. Among methods of delivery manual extraction of the after-coming head and difficult forceps deliveries are especially dangerous. The mechanism of hemorrhage consists in pressure upon the flat bones of the cranium, producing a passive stretching of the duplications of the dura, accompanied by increased tension in the circulation. In studying these cases at autopsy, the circulation being injected, the point of hemorrhage can readily be found owing to the fact that the tissues retract. Particularly the longitudinal sinus and the veins of the tentorium are especially apt to bleed. The frequency and importance of these lesions, to which attention has already been called by others, are thus emphasized.

Placental Infarcts.—McNALLEY (*Am. Jour. Obst. and Gynec.*, 1924, **8**, 186) has studied 1352 placentæ with regard to the presence of white infarcts. He groups these infarcts in three classes. First are those which on close examination are found to be small masses of fibrin which have replaced a previous collection of blood. All the white infarcts on the fetal surface of the placenta belong to this class, as do many of the intraplacental and some of those seen on the maternal surface. They are not organized, but are caused by the laying-down of fibrin as a laminated clot. The second class is red in the beginning, but becomes white later. These may properly be called red infarcts. All large infarcts belong to this class and, in fact, most of those visible to the naked eye. These seem to be associated with the toxemia of pregnancy. The third class represent senile placental changes. A point of difference is found in the senile changes of the syncytium, which occur along with those in the bloodvessels and result in a deposition of fibrin about the periphery which cuts off the blood supply and produces necrosis.

The Use of Pituitary Extract in Obstetrics.—BURGUR (*Gynéc. et Obst.*, 1924, **9**, 136) describes his experiences in the Strasburg Clinic in the use of pituitary extract. He quotes the literature upon the subject, describes cases in which pituitrin acted well and states that he has used pituglandol in doses 1 cc and pituitrin in doses of 0.5 cc, as the intensity of the action is proportioned to the quantity injected. He gives small doses, one-half or one-third of the usual doses, repeated as often as necessary. The result of the drug should be obtained in a little less than an hour after it is given. It is rapidly eliminated so that one can repeat a dose in about an hour without danger. The number of doses given by various observers has reached, in one instance, twenty. He devotes considerable space to the accidents following the use of pituitrin, notably rupture of the uterus and has collected a large series of cases. He would use the drug at the end of the period of dilatation or, better still, conditions being favorable, during the period of expulsion. The presenting part must be well in the pelvis and there should be no retraction of the fetal part between pains. He believes that in most of these cases feeble uterine contraction indicates a spastic condition of the uterine muscle rather than exhaustion. He often combined a small dose of morphin with pituitary extract to reduce the element of spasm and violent uterine action. Cases of disproportion and pelvic contraction should be recognized by the general practitioner as complicated

and dangerous, and should be promptly referred to the hospital under the care of obstetricians. He urges that in cases where grave complications exist, due weight be given to these complications as well as to the administration of pituitrin in deciding the cause of an accident. Admitting that the improper use of pituitrin frequently causes fatal accidents, there may still be other factors in a given case which are of importance. It goes without saying, he remarks, that midwives should be strictly forbidden to use pituitary extract in any form. In skilful hands the drug may render valuable service and, equally, injury by improper administration. The writer urges that accidents in its use should be accurately described and published, so that the profession may learn the truth concerning this valuable substance.

Painless Child-birth by Synergistic Methods.—GWATHMEY (*Am. Jour. Obst. and Gynec.*, 1924, **8**, 154) adds 200 to his 100 cases previously reported, treated by this method. He states that he has changed his formula nineteen times, but has made no alteration in the last 100 cases. At presen this method is as follows: The patient receives from one to three hypodermics and one rectal instillation. The first hypodermic, ½ grain morphin dissolved in 2 cc of a 50 per cent solution of magnesium sulphate, is given when labor is well established, pains four to five minutes apart, lasting thirty or more seconds. No more morphin is given, but by rectum there is administered a mixture of 2½ ounces of ether, 10 gr. of quinin hyprobromate in 2 drams of alcohol with enough olive oil to make 4 ounces. The doctor or nurse comes in contact with the patient often only twice; at most four times. The magnesium sulphate is in 2-cc ampules 50 per cent strong. If the first hypodermic has a marked effect, rectal treatment is given in one or two hours; if not, it is given within fifteen or twenty minutes. The effect of the combined treatment is usually seen with fifteen minutes and lasts about four hours. If needed, 2 cc 50 per cent magnesium sulphate are given hypodermically in addition once or twice. Noise is avoided as much as possible and the patient kept as quiet as possible. The author states that no method could possibly be safer or simpler, which is certainly an exhibition of sublime faith and self-confidence. Additional notes are given upon other methods, which serve to illustrate the perfection of that already described.

A Natural Immunity in the Newborn.—MUSSELMAN (*Am. Jour. Obst. and Gynec.*, 1924, **8**, 45, 141) has studied this subject in the New Haven Clinic and quotes from the literature regarding it. It seems to be established that the human maternal serum has greater power to destroy bacteria than that of the newborn. This serum has a greater content of complement than that of the newborn. In maternal serum there is no parallel relationship between the condition of the serum of the mother and the child. Pregnancy itself does not cause an increase in the effectiveness of maternal serum. The difference is due to an actual deficiency in the serum of the newborn because it possesses an anti-complementary substance. Colostrum and milk have very little—if any—power to destroy bacteria. The power of serum as a germicide does not depend along upon its complement, but is greatly increased by it. These studies indicate that the infant is only partially, if at all, dependent upon its mother for antibodies or natural immunity.

GYNECOLOGY

UNDER THE CHARGE OF

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Acute Ulceration of the Vulva.—Under this heading McDONAGH (*Brit. Jour. Dermat. and Syph.*, 1924, **36**, 285) includes two clinical conditions: (1) Acute ulceration due to Doederlein's bacillus and (2) acute ulceration due to Vincent's organism which is frequently called *vulvitis erosiva et gangrenosa*. Both types of ulceration are rare and are due to organisms which are naturally saprophytic. An infection is caused only when the patient's general resistance is lowered or the local resistance has been damaged by uncleanliness, disease or trauma. These two clinical conditions are nonvenereal in nature and they are most prone to attack virgins. The author has not seen a case in a woman over thirty years of age. Both types of ulceration, especially in the former, may show a tendency to relapse. For the ulceration due to the Doederlein bacillus, or Bacillus crassus, there is no specific treatment, but the ulceration occasioned by the Vincent organism clears up rapidly under arsphenamin and relapses only when too many injections of this drug are prescribed. The form of ulceration due to the Bacillus crassus may be divided into two clinical types, of which the former is the more common: (1) Very acute, small and multiple ulcers, ushered in with rigors, fever, etc.; (2) less acute, larger and deeper ulcers unassociated with subjective symptoms. In the five cases of this type in this series there was no evidence of an erosion preceding the ulcer. The initial lesion appears to be an ulcer, which from the very beginning attacks the deeper tissue, hence the reason why the ulcers have a grayish-white appearance, and are covered with pus and stringy material, which is removed with difficulty. The most common sites to be involved are the inner surfaces of the labia. The ulcers are extremely painful, but there is little discharge and no lymphadenitis. The facts that the ulcers are not preceded by erosions, that they do not usually cause great destruction of tissue and that they do not emit a characteristic odor, serve to differentiate this form of ulceration from that occasioned by Vincent's organism. The acute ulceration due to Vincent's organism may occur *de novo* or appear as a superinfection, but is always ushered in with severe constitutional disturbances. There is often considerable discharge which gives off a very characteristic odor. The inguinal lymphatic glands are generally swollen and painful. The organism is easy to find and is not difficult to culture, the cultures also having a most offensive odor. In an incredibly short space of time a great destruction of tissue may occur. If the parts are left uncovered, exposed to the air and fre-

quently bathed with hydrogen peroxide the condition heals up, because the organism requires anaërobic conditions. Healing is expedited by two injections of arsphenamin, but if this number is exceeded the ulceration may relapse and spread with renewed vigor, clearly showing that treatment acts by stimulating the patient's resistance and not directly upon the microörganisms.

Clinical Study of Hypernephroma.—On reviewing the literature of hypernephroma, CUTLER (*Bull. Johns Hopkins Hosp.*, 1924, **35**, 214) was struck by the scarcity of clinical data recorded relative to these tumors, although the pathology of these tumors has been carefully studied. He found that the occurrence of hypernephroma is comparatively rare, since at the Johns Hopkins Hospital there were only 32 cases which came to operation during a period of sixteen years, the average age of the patients being fifty-one years. The condition is practically twice as common in the male as in the female. The average duration of symptoms from the time of appearance of the first symptom to the time of operation in this series was three and a half years. Hematuria is by far the commonest symptom of the disease, being rarely absent and in half of the cases it is the initial symptom. Pain was the second commonest symptom and is usually a localized soreness or discomfort in the kidney region, and is quite distinct from the pain associated with renal colic. Renal colic occurred in 20 of the 30 cases in which its presence or absence was mentioned. In the majority of instances the pain was associated with the passage of long, wormlike blood clots and the colic was undoubtedly due to blocking of the urinary passages by these clots as the pain was relieved immediately after the clots were passed. Dysuria and retention were present in 7 of the 32 cases. When hemorrhage from the tumor was sufficiently extensive blood clots formed, which by filling the bladder produced a marked dysuria and retention. Frequency of urination was present in only 4 of the cases, thus this symptom is rare in this condition as compared to its frequency in tumors of the bladder. Hematuria, on the other hand is a common initial manifestation in both conditions, therefore the presence or absence of frequency of urination in a patient complaining of hematuria may serve as a useful differential point in the history between the two conditions. A tumor mass is usually palpable and it is not at all uncommon to have renal calculi associated. Regarding all temperatures of 99° or over as febrile, this series showed 75 per cent of the cases to be febrile although the elevation of temperature was rarely over 100°. The phenolsulphonephthalein test shows a marked decrease in excretion on the diseased side and pyelography has been of very great help in the diagnosis of kidney tumors, the majority, but not all, of the kidney tumors producing markedly noticeable distortion of the kidney pelvis.

Operative Cure of Pruritus Ani and Vulvæ.—One of the most annoying and refractory conditions which the gynecologist is called upon to treat is the intense vulvar and anal itching, for which no cause can be found. ALLEN (*New Orleans Med. and Surg. Jour.*, 1924, **76**, 532) again describes his method of treating these cases which has been quite satisfactory in practically every case on which it was tried.

The operation consists of the separation of the skin from the underlying tissue, thus dividing all nerves which reach the affected parts, rendering these parts anesthetic and preventing the skin from immediately healing to the underlying tissues by packing, which is kept up until a firm bed of granulation has formed, which usually requires about one week. When the packing is discontinued the skin is allowed to fall back into place, where it soon is again firmly united, leaving an anesthetic area which nearly equals the extent of the undermined area, which gradually diminishes in size, but is not followed by a return of the pruritus. The operation on the anal region is the simpler. The area involved must first be accurately determined and then a series of incisions is made beginning at the anal margin and continuing outward to about ½ inch beyond the affected area, which rarely exceeds 2 inches. These incisions are made about 1 inch apart at their peripheral extremities until the entire peri-anal region has been covered. These skin strips are now dissected up, preferably with a scalpel, except at their two ends, which are left attached. In separating the skin from the subcutaneous tissues, a small margin of tissue is left attached to its under surface to insure sufficient circulation to prevent sloughing. As the pruritic area rarely involves the mucous surfaces, the incisions need not invade them. The space beneath the flaps is packed with gauze as described above and frequent sitz baths, with a liberal supply of soap, are insisted on as after-treatment. The packs may need changing, but often remain *in situ* for the full period of one week. The operation sounds logical, and the author is so enthusiastic about it that it would be well to bear it in mind when we are called upon to treat this distressing condition.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF
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Hearing in the Presence of a Noise.—Many deaf persons, with middle ear trouble, say that they "can hear better in a noise," this noise being the noise of a street car, an elevated train, a machine shop or some similar type of disturbance. The observations which have been actually made seem to be based on the fact that these persons can carry on a conversation with a normal hearing person more easily in a noise than otherwise. KRANZ (*Ann. Otol., Rhinol. and Laryngol.*, 1924, **33**, 283) conducted a number of tests on this type of deafness by talking to the subject in a monotone, repeating over and over some phrase and either (1) using a telephone receiver which was emitting a loud tone of 120 cycles per second and alternately placing it near to his ear (1 to 3 inches) and taking it away, or (2) using a specially

designed bone-conduction type of telephone receiver actuated by a 120-cycle current and alternately placing this on his head and taking it off, there being sufficient intensity to give the person a loud subjective sound when on his head. By these procedures it was learned that the presence of the disturbance caused by either the bone or air conducted sound did not in any case result in any improvement in the subject's ability to hear or to understand the phrases being spoken. The author states that, seemingly, the determining factor in the ability of some deaf persons to converse better in a noise than otherwise is undoubtedly the increased loudness with which a normal person talks in the presence of a noise. The normal person, of course, tries to talk so that the sound of his voice will predominate over the disturbing noise as judged by his own hearing. The actual ratio of the objective intensities of the speech and the disturbing noise striking the ear is the same for the normal and the deaf individual, but due to the difference in the acuity of the two persons the speech sound will for the deaf person be much farther above the low limit of audition as compared with the disturbing noise than will be the case for the normal person. Another factor is the difference in frequency between sounds concerned in speech and those of noise. The latter are probably of much lower frequency than the former, and it is also a fact that people with middle-ear trouble are particularly deaf at low frequencies. The noise bothers the deaf person less than it does the normal person.

The Tympanic Presclerosis of Citelli.—As reviewed by CALDÉRIN (*Rev. españ. de. laringol.*, Madrid, 1924, **25**, 220) this condition, which affects for the most part older children but also infants, is important inasmuch as it indicates impending otosclerosis. Occurring in those with adenoids, it is seen particularly in cases who have further impairment of audition following adenoidectomy. In many instances a familial history of otosclerosis can be elicted and divers constitutional defects are present. Higher tones are heard better than lower tones. Air conduction is diminished. Normal mobility of the ossicular chain obtains; the Eustachian tube is patulous and local findings fail to account for the impaired hearing, which would seem to result from changes in the bones around the tympanic cavity and labyrinth. As with so many other states, cure depends on early diagnosis and treatment. As suggested by Citelli, calcium in combination with preparations of iodin and peptone provide efficient therapeutic measures.

Bacteriologic Study of Middle-ear Infections.—VALENTINE (*Jour. Infect. Dis.*, 1924, **35**, 177) conducted a series of investigations in cases of acute and chronic otitis media to ascertain: (1) The relative frequency of the different bacterial varieties; (2) the bacterial flora of the aural discharge in acute cases at intervals over a considerable period of time; (3) the throat flora in acute respiratory infections prior to development of an ear condition in order to trace bacteriologically the source of the otitic infection; (4) the throat flora in all cases of otitis media at the time of the original paracentesis and also later to determine whether the anatomical, clinical and bacteriological picture of the throat had any relation to the severity and subsequent history of the ear condition; (5) the bacterial variety found in the majority

of acute cases to learn if there was a specific serological variety which had a peculiar affinity for an elective localization in the ear; (6) the ultimate condition of chronicity or deafness in the acute cases from the standpoint of the original bacterium found in the ear infection (the relation of the different varieties of secondary invaders to the final condition of chronicity). Extensive and detailed observations were recorded on 100 acutely infected middle ears in 77 cases and on the aural discharge from 12 chronic cases. It was found that the beta-hemolytic streptococcus was the microörganism most frequently encountered, occurring in 53 per cent of the acute cases, while staphylococcus was encountered alone or with other bacteria in about 30 per cent. Pneumococci, green streptococci and diphtheroid bacilli predominated in a small percentage of cases. In the chronic group diphtheroid bacilli, staphylococci, Bacillus pyocyaneus, Bacillus proteus and Bacillus coli were obtained in pure or mixed culture. In those cases in which hemolytic or green streptococci or pneumococci were found the same bacterial species were also found in the throat. In 9 cases studied the *same serological* variety of streptococcus were present in the throat and the *ear discharge*. In most cases cultures made from the aural discharge several days or a week after paracentesis showed that the apparent etiological bacterium had become reduced in number, while the proportion of the other varieties had increased. In 19 out of 22 cases of bilateral otitis media, involved at approximately the same time, the same bacterial species were obtained in the primary culture from both ears in each individual. The heterogenicity of the strains isolated from the majority of acute middle-ear infections indicated the absence of a common primary or secondary causative agent. In the cases studied over a considerable period of time diphtheroid bacilli and staphylococci were found to be the most frequent secondary invaders in the ear discharges after the acute stage of the infection. There was some indication that in certain cases these bacterial varieties may have been factors responsible for the chronicity of the inflammatory process. The authoress concluded by saying that "The presence of numerous serological varieties of beta-hemolytic streptococci as the apparent etiological organisms in a series of middle-ear infections indicates that the use of a stock streptococcus vaccine is probably of little or no specific value. However, an autogenous vaccine made from the original variety in the ear discharge should be tried."

The Etiology of Ozena.—Nasso and Tassi (*Pediatria*, 1924, **32**, 1065) succeeded in isolating from the filtrate of crusts and nasal secretions of 24 persons, with ozena, a tiny, nonmotile, Gram-positive microörganism. This bacterium could be cultivated, both aërobically and anaërobically in catalyzing mediums of the Tarozzi-Noguchi type. When inoculated into rabbits—either intravenously or locally in the nasal submucosa, the organism produced a condition characterized by mucopurulent secretion, crust formation and abnormal widening of the nasal fossæ. A bacterium, identical with that injected, could be recovered from the filtrate of the nasal secretion of the inoculated rabbits. In the blood serum of individuals suffering with ozena, as well as of the experimentally infected animals, specific agglutinin and amboceptors for the microörganism could be demonstrated.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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A Case of Early Cancer Arising from Ulcer of Stomach.—Moszkowicz (*Virchows Archiv*, 1924, **253**, 511) reports the finding of a small ulcer along the lesser curvature of the stomach, which showed the typical characters of the common peptic ulcer. In the routine examination of this specimen the surgical diagnosis was substantiated. Only upon more minute analysis and further serial section of the ulcer was a small cancerous invasion discovered along one border of the ulcer. This tumor showed colloid degeneration and the cells composing it formed tubular structure different from the normal neighboring mucosa which it undermined and displaced. Occasional small islands of aberrant epithelial masses were also found in the deeper portions of the stomach wall where the atypical characters were still more pronounced. The author is convinced that he is dealing with a true cancer of early development, and arising in an old gastric ulcer. The case illustrates well the care which must be taken in examining gastric ulcer to exclude the possibility of cancerous growth in the tissues.

Spontaneous Rupture of the Aorta.—Letterer (*Virchows Archiv*, 1924, **253**, 534) reports 2 cases of young individuals in whom rupture of the aorta had occurred. Both were men, aged thirty-nine and twenty-eight years, respectively. In one of them there was a history of injury, the individual falling from a height during athletic exercises. In the other case the individual gave a history of handling heavy boxes although no direct relation between his work and the injury could be traced. The rupture of the aorta in one took place immediately above the aortic ring and in the other in the descending arch. In both instances the tears were clean cut and the author was unable to find any local lesion in the wall to account for unusual weakness. Marked hypertrophy of the heart and peripheral arteriosclerosis was present in the 1 case but absent in the other. The history in both cases is too indefinite to account for the rupture, and the absence of changes in the aortic wall gives no clue for the localization of the injury. The aorta showed no constriction above the entrance of the ductus arteriosus. The author believes that two main factors play a part in the rupture: (1) Sudden increase in blood pressure, and (2) tugging of the heart through compression or distortion of the body.

Lipoid Analyses in the Adrenals of Cattle.—Sorg and Jaffe (*Centralbl. f. allgem. Path.*, 1924, **35**, 353) undertook a histochemical analysis of the adrenals of both male and female animals and found that they were unable to isolate cholesterolester or any of the cholesterin

compounds but, on the other hand, varying quantities of lipoids were distinguishable. These results have been repeatedly verified in the microchemical analyses of various investigators. Chemical extraction showed the presence of small quantities of cholesterin. Somewhat similar results were obtained in the analysis of corpora lutea. The lipoids in the adrenals are similar to those found in the sex glands. The chemical characters of the content of these various tissues is very similar and the small quantities of cholesterin which could be isolated from them was found to be in the free and not the combined state. They believe that these small quantities of cholesterin are the results of a cell disintegration rather than cell metabolism. They come to the conclusion that combined cholesterin plays no part in cattle in the metabolism of lipoids.

The Production of an Exotoxin by Certain Strains of Staphylococcus Aureus. — Dick and Dick's demonstration of a dermotoxic poison from scarlet fever strains of streptococcus hemolyticus prompted PARKER (*Jour. Exp. Med.*, 1924, **40**, 761) to search for a similar poison in Staphylococcus aureus. She succeeded in demonstrating in sterile filtrates of broth cultures of certain strains of Staphylococcus aureus, a powerful poison with a selective action for the skin. The relationship of this poison with leukocidins was not investigated. Four out of twenty-one strains showed the poison, the work being carried out on rabbits. One of the rabbit-negative strains produced an effect in the human skin similar to the Dick reaction. The medium used was a well-buffered broth solution containing a small amount of glucose. The presence of glucose (or probably the acids resulting from its breakdown) had an inhibiting effect on poison production. The toxin could be demonstrated in sterile Berkefeld filtrates of twenty-four hour cultures but the most toxic poisons were obtained after four to six days' growth. The toxicity of filtrates was tested by intracutaneous and subcutaneous inoculation, all inoculations being controlled. The reaction, which is described in detail, was always characteristic and systemic toxic symptoms were observed. The histological changes in the skin reactions are reported. Intravenous injection of the poison was tried but irregular results were obtained. The toxin studied seemed to be identical from all strains, was definitely thermolabile and produced an antitoxin which was not present in the sera of normal rabbits. This antitoxin was produced in very small quantities if at all, in using the intravenous route of immunization. The work is still being carried on and further communications on this interesting study may be looked for.

The Complement-fixation Test in Tuberculosis.—A comprehensive survey of the previous work done and the conclusions reached is given by WILLIAMS and BRYCE (*Jour. Path. and Bact.*, 1924, **28**, 401). Following this they outline the standard that must be attained before the test can be made use of diagnostically. They base their observations and conclusions on the examination of over fifteen months. The technic used was that described by Harrison for the Wassermann test. Various antigens were used, the details of which are given. Three groups of sera were used. The first from proved cases of tuberculosis, the presence of bacilli in sputum, urine, tissues, or guinea pigs being accepted as

proof. These cases gave 74.4 per cent of positive results. The second group was from a few healthy adults and from a large number of hospital patients in whom there was no reason to suspect tuberculosis. Five per cent of these gave positive results and in all but one of these it was impossible to exclude the possibility of tuberculosis. In this connection, the authors examined a series of 500 individuals, which included many of the foregoing group, for skin allergy, 66.6 per cent were found to react positively to the von Pirquet test. Their explanation of the difference in the results of the tests is the assumption that the complement-fixation reactions indicate active disease rather than previous infection and that those giving positive von Pirquet reactions have been at some time infected and have been able to resist it. They consider that this does not weigh against the specificity of the test. The last group was of clinically certain tuberculosis where bacteriological proof was lacking, and of suspected tuberculosis where aid in diagnosis was sought. Of these 50 per cent of pulmonary cases, 18.5 per cent of bone cases and 40 per cent of a heterogeneous series gave positive complement-fixation results. The fact that no bovine strain was present in the antigen may explain certain negative results. From their study they conclude that the test is specific but that it is not completely satisfactory as a diagnostic agent. While a negative result does not exclude tuberculosis, a strongly positive reaction is, with few exceptions, evidence of the disease in an active form. Finally, the routine performance of the Wassermann test simultaneously with it draws attention to the possibility of a syphilitic basis for the lesions present in some cases suspected of being tuberculous.

The Differentiation of Two Distinct Types of Phagocytic Cells in the Spleen of the Rabbit.—CUNNINGHAM, SABIN and DOAN (*Proc. Soc. Exp. Biol. and Med.*, 1924, **21**, 179) anesthetized a rabbit and exposed the spleen. By splenic puncture blood and tissue cells were obtained and studied in supravital films with neutral red and Janus green staining. Two types of phagocytic cells were found: (1) Monocytes of the circulating blood and (2) macrophages, histiocytes or clasmatocytes, the former forming 17 per cent of the splenic cells and the latter 1 per cent. The clasmatocytes are large cells with relatively small oval nuclei, located toward the periphery of the cells. They react intensely to neutral red and the aggregations of the stain are scattered irregularly throughout the cytoplasm. They contain a few or no mitochondria. The monocytes are somewhat smaller in size with relatively larger, horse-shoe, or kidney-shaped nuclei. There is a clear space in the cytoplasm surrounded by a rosette of small, radiating aggregations of neutral red. Mitochondria are always present and are brilliantly stained with Janus green. The pattern of the monocytes is quite specific and is only occasionally obscured when the cells are in active motion. Both types of cells are phagocytic for red blood corpuscles. When a corpuscle is ingested by a monocyte it is placed in the periphery of the rosette of neutral red granules without disturbing the arrangement. But in the clasmatocyte such a corpuscle is placed adjacent to the nucleus on the side having the most cytoplasm. The monocyte arises from a "stem cell" of mesenchymal origin in the pulp, where there is no endothelium whatever; while the clasmatocyte arises from the endothelium of the sinuses.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Incidence of Certain Communicable Diseases Common among Children.—COLLINS (*Pub. Health Rep.*, 1924, **39**, 1553) summarizes his studies based on observations of school children as follows: "In the course of certain studies in child hygiene, information was obtained from approximately 35,000 school children from five to nineteen years of age as to whether they had ever had measles, whooping cough, mumps, chicken pox, scarlet fever, or diphtheria. The children were classified according to age, sex, color, and nativity or nativity of the parents. The curves of the percentage of children who had had an attack of these diseases at some time in their lives rises fairly rapidly as age increases until about the thirteenth or fourteenth year, after which time the rise is very slow, except in the case of mumps, which continues to rise considerable through the nineteenth year. The slackening in the rate of increase presumably means that the susceptible material is largely used up. When the annual incidence was considered it was found that for the ages studied the maximum incidence of measles was at six to seven years; whooping cough, five to six years; mumps, seven to nine years; chicken pox, five to six years; scarlet fever, eight to ten years; and diphtheria, five to seven years. As age increases, within the limits of those included in this study, the annual incidence rapidly declines. By the time the adult ages were reached, about 89 per cent of the children had had measles, about 78 per cent had had whooping cough, 65 per cent mumps, 52 per cent chicken pox, 12 per cent scarlet fever, and 9 per cent diphtheria. Measles, whooping cough, chicken pox, and scarlet fever seem to have been more prevalent among girls than among boys. The rates for mumps and diphtheria are about the same for the two sexes. Measles, whooping cough, mumps, and chicken pox seem to have been more prevalent among the native white than among the foreign children. The rates for scarlet fever and diphtheria seem to be about the same for the two groups. Measles, chicken pox, scarlet fever, and diphtheria seem to have been more prevalent among the white than among the colored. The rates for mumps were possibly higher among the colored. Whooping cough seemed to be about the same in both groups."

Per Capita Medicinal Requirements of Narcotics.—DUMEZ (*Pub. Health Rep.*, 1924, **39**, 2358–2360) endeavored to ascertain, by visiting physicians, dentists, pharmacists, and so forth, the legitimate requirements for opium and coca leaves for a population of about 70,000.

Reducing the figures to a per capita basis it was found that 6.98 grains of opium were sold and 29.32 grains of coca leaves. This indicates that for the United States 105,697 pounds of opium and 443,988 pounds of coca leaves would be required per year.

Mortality from Malaria.—MAXCY (*Pub. Health Rep.*, 1924, **39**, 2559–2561) has studied the mortality from malaria in the southern states and finds in general a sustained decrease and considers that the evidence pointing to the gradual disappearance of the disease is encouraging.

Plague.—The Public Health Service.—(*Pub. Health Rep.*, 1925, **40**, 51) reviews the history of plague, with special reference to the present pandemic. It is pointed out that nothing short of interference that would paralyze commerce will eliminate the risk of the spread of the disease on vessels. Rat infection in cities may require many years for eradication. Even the pneumonic form is traceable eventually to rodents. The necessity for rat-proof buildings is pointed out and the statement made that the rat must be built out of existence. The recent outbreak of plague, both pneumonia and bubonic, in Los Angeles (*Pub. Health Rep.*, 1925, **40**, 191) has brought to the front the fact that we have in the United States an endemic form of rodent plague which signifies the necessity for a persistent campaign. The spread of plague foci is regarded as of greater significance and it is pointed out that these have increased in the last half-century so that no longer may we regard as menaces only the remote classic foci in Asia and Africa. The world distribution is given for a period of years and special stress is laid on seasonal prevalence.

Rocky Mountain Spotted Fever: Non-filterability of Tick and Blood Virus.—SPENCER and PARKER (*Pub. Health Rep.*, 1924, **39**, 3251–3255) give the following summary: (1) The virus of Rocky Mountain spotted fever as it occurs in the blood of guinea pigs and in emulsions of infected tick viscera (adults and nymphs) will not pass Berkefeld "N" and "V" filters. (2) Inoculation of filtrates of blood or tick virus does not produce immunity in guinea pigs. (3) The coarse "V" filters that hold back the virus of Rocky Mountain spotted fever will readily pass broth cultures of *Staphylococcus aureus*. (4) The failure of the virus to pass Berkefeld filters does not appear to be due to a chemical affinity for or adsorptive property of the material of which the filter candles are made.

A Study of the Pellagra-preventive Action of Dried Beans, Casein, Dried Milk, and Brewers' Yeast, with a Consideration of the Essential Preventive Factors Involved.—GOLDBERGER and TANNER (*Pub. Health Rep.*, 1925, **40**, 55–78) review some phases of their studies on pellagra which throw fundamental light on an obscure corner of etiology. The following elements of diet are considered: Soy beans and California black-eye peas were inadequate to prevent pellagra. Casein appeared to have a good effect on general nutrition and prevented or delayed the development of the dermatitis; it failed, however, to prevent some of the other symptoms and signs of the disease. Dried skim milk seems to have some pellagra-preventive action. Brewers' yeast appeared to be of great value in preventing the disease. The following conclusions are

drawn: (*a*) A liberal supply of protein, presumably of good biological quality, does not completely prevent, though it may modify, the clinical picture of pellagra by notably delaying or preventing the development of the distinctive dermatitis. This modifying action may be of an indirect, sparing nature. (*b*) In the prevention (and presumably causation) of pellagra there is concerned a heretofore unrecognized or unappreciated dietary factor which we designate as factor *P–P*. This may be effective with but little, possibly without any, coöperation from the protein factor. (*c*) Factor *P–P* may possibly play the sole essential role in prevention (and causation) of pellagra. (*d*) Factor *P–P* is present in brewers' yeast, in milk and (on the basis of our experience with fresh meat) in lean beef; it is very low, or lacking, in dry soy beans, dry cowpeas, butter, cod-liver oil and canned tomatoes.

The Epidemic Outbreak in Japan.—SYDENSTRICKER (*Pub. Health Rep.*, 1924, **39**, 3215–3219) presents the available data on an apparently hitherto unrecognized disease having points of similarity to epidemic poliomyelitis, lethargic encephalitis and cerebrospinal meningitis. The epidemic was explosive in nature and lasted three or four months, beginning in July. The disease appears to be slightly or not at all contagious. The onset of temperature is sudden and the fever may go to 41° C.; nausea, vomiting and insomnia may occur. The temperature reaches normal in from about eight to fifteen days. There is a spastic condition of upper and lower extremities and strongly marked Kornig sign; no Babinski nor Oppenheim sign. Pulse is slow in relation to the temperature. Unconsciousness or deep somnolence is a predominant symptom; in severe cases coma occurs, sometimes delirium. Petechial hemorrhages have been noted on the backs of patients. The only laboratory findings of note are a spinal fluid cell count of 10 to 40 and a marked increase in polymorphonuclear neutrophiles. At autopsy there is congestion and edema of meninges and parenchymatous degeneration of liver and kidneys. Cultures were negative. The disease was reproduced in rabbits by subdural injection of filtrates.

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